FIRST AID FOR THE® USMLE® STEP 1

2017

A STUDENT-TO-STUDENT GUIDE

- 1,300+ frequently tested facts and mnemonics
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Dedication

To the contributors to this and past editions, who took
time to share their knowledge, insight, and humor for the
benefit of students and physicians everywhere.

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Contents

Contributing Authors vii
Associate Authors viii
Faculty Advisors ix
Preface xi
Special Acknowledgments xii
General Acknowledgments xiii
How to Contribute xvii
How to Use This Book xix
Selected USMLE Laboratory Values xx
First Aid Checklist for the USMLE Step 1 xxii

▶ SECTION I GUIDE TO EFFICIENT EXAM PREPARATION 1

Introduction 2
USMLE Step 1—The Basics 2
Defining Your Goal 12
Excelling in the Preclinical Years 13
Timeline for Study 14
Study Materials 18
Test-Taking Strategies 20
Clinical Vignette Strategies 21
If You Think You Failed 22
Testing Agencies 22
References 23

▶ SECTION I SUPPLEMENT SPECIAL SITUATIONS 25

▶ SECTION II HIGH-YIELD GENERAL PRINCIPLES 27

How to Use the Database 28
Biochemistry 31
Immunology 91
Microbiology 119
Pathology 203
Pharmacology 223
Public Health Sciences 245

SECTION III HIGH-YIELD ORGAN SYSTEMS 263

Approaching the Organ Systems 264
Cardiovascular 267
Endocrine 311
Gastrointestinal 343
Hematology and Oncology 385
Musculoskeletal, Skin, and Connective Tissue 423
Neurology and Special Senses 459
Psychiatry 523
Renal 547
Reproductive 579
Respiratory 625
Rapid Review 651

SECTION IV TOP-RATED REVIEW RESOURCES 671

How to Use the Database 672
Question Banks 674
Question Books 674
Web and Mobile Apps 674
Comprehensive 675
Anatomy, Embryology, and Neuroscience 675
Behavioral Science 676
Biochemistry 676
Cell Biology and Histology 677
Microbiology and Immunology 677
Pathology 677
Pharmacology 678
Physiology 679
Abbreviations and Symbols 681
Image Acknowledgments 689

Index 711
About the Editors 777

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Preface

With the 27th edition of *First Aid for the USMLE Step 1*, we continue our commitment to providing students with the most useful and up-to-date preparation guide for the USMLE Step 1. This edition represents an outstanding revision in many ways, including:

- 30+ entirely new facts with continued expansion of quality improvement principles, safety science, and healthcare delivery to align more closely with the USMLE Content Outline.
- Hundreds of major fact updates culled from thousands of student and faculty contributions.
- Extensive text revisions, new mnemonics, clarifications, and corrections curated by a team of more than 25 medical student and resident physician authors who excelled on their Step 1 examinations and verified by a team of expert faculty advisors and nationally recognized USMLE instructors.
- Complete reorganization of the neurology chapter to better distinguish normal physiology from neuropathology and to emphasize the special senses.
- Improved Rapid Review section with page numbers to the text, to quickly find these high-yield concepts in context.
- Updated with more than 100+ new or revised full-color photos to help visualize various disorders, descriptive findings, and basic science concepts. In particular, imaging photos have been labeled and optimized to show both normal anatomy and pathologic findings.
- Updated with dozens of new and revised diagrams. We continue to expand our collaboration with USMLE-Rx (MedIQ Learning, LLC) to develop and enhance illustrations with improved information design to help students integrate pathophysiology, therapeutics, and diseases into memorable frameworks.
- A revised exam preparation guide with updated data from the USMLE and NRMP. The guide also features new evidence-based techniques for efficient and effective test preparation. The updated supplemental guide for IMGs, osteopathic and podiatry students, and students with a disability can be found at our blog, **www.firstaidteam.com**.
- An updated summary guide to student-recommended USMLE Step 1 review resources, including mobile apps for iOS and Android. The full resource guide with detailed descriptions can be found at our blog.
- Real-time Step 1 updates and corrections can also be found exclusively on our blog.

We invite students and faculty to share their thoughts and ideas to help us continually improve *First Aid for the USMLE Step 1* through our blog and collaborative editorial platform. (See How to Contribute, p. xvii.)

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How to Contribute

This version of *First Aid for the USMLE Step 1* incorporates thousands of contributions and improvements suggested by student and faculty advisors. We invite you to participate in this process. Please send us your suggestions for:

- Study and test-taking strategies for the USMLE Step 1
- New facts, mnemonics, diagrams, and clinical images
- High-yield topics that may appear on future Step 1 exams
- Personal ratings and comments on review books, question banks, apps, videos, and courses

For each new entry incorporated into the next edition, you will receive up to a **$20 Amazon.com gift card** as well as personal acknowledgment in the next edition. Significant contributions will be compensated at the discretion of the authors. Also, let us know about material in this edition that you feel is low yield and should be deleted.

All submissions including potential errata should ideally be supported with hyperlinks to a dynamically updated Web resource such as UpToDate, AccessMedicine, and ClinicalKey.

We welcome potential errata on grammar and style if the change improves readability. Please note that *First Aid* style is somewhat unique; for example, we have fully adopted the *AMA Manual of Style* recommendations on eponyms ("We recommend that the possessive form be omitted in eponymous terms") and on abbreviations (no periods with eg, ie, etc).

The preferred way to submit new entries, clarifications, mnemonics, or potential corrections with a valid, authoritative reference is via our website: **www.firstaidteam.com**.

This website will be continuously updated with validated errata, new high-yield content, and a new online platform to contribute suggestions, mnemonics, diagrams, clinical images, and potential errata.

Alternatively, you can email us at: **firstaidteam@yahoo.com**.

Contributions submitted by **May 15, 2017**, receive priority consideration for the 2018 edition of *First Aid for the USMLE Step 1*. We thank you for taking the time to share your experience and apologize in advance that we cannot individually respond to all contributors as we receive thousands of contributions each year.

NOTE TO CONTRIBUTORS

All contributions become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. Contributions should be supported by at least two high-quality references.

Check our website first to avoid duplicate submissions. In the event that similar or duplicate entries are received, only the first complete entry received with valid, authoritative references will be credited. Please follow the style, punctuation, and format of this edition as much as possible.

JOIN THE FIRST AID TEAM

The *First Aid* author team is pleased to offer part-time and full-time paid internships in medical education and publishing to motivated medical students and physicians. Internships range from a few months (eg, a summer) up to a full year. Participants will have an opportunity to author, edit, and earn academic credit on a wide variety of projects, including the popular *First Aid* series.

For 2017, we are actively seeking passionate medical students and graduates with a specific interest in improving our medical illustrations, expanding our database of medical photographs, and developing the software that supports our crowdsourcing platform. We welcome people with prior experience and talent in these areas. Relevant skills include clinical imaging, digital photography, digital asset management, information design, medical illustration, graphic design, and software development.

Please email us at **firstaidteam@yahoo.com** with a CV and summary of your interest or sample work.

How to Use This Book

CONGRATULATIONS: You now possess the book that has guided nearly two million students to USMLE success for over 25 years. With appropriate care, the binding should last the useful life of the book. Keep in mind that putting excessive flattening pressure on any binding will accelerate its failure. If you purchased a book that you believe is defective, please **immediately** return it to the place of purchase. If you encounter ongoing issues, you can also contact Customer Service at our publisher, McGraw-Hill Education, at https://www.mheducation.com/contact.html.

START EARLY: Use this book as early as possible while learning the basic medical sciences. The first semester of your first year is not too early! Devise a study plan by reading Section I: Guide to Efficient Exam Preparation, and make an early decision on resources to use by checking Section IV: Top-Rated Review Resources. Note that *First Aid* is neither a textbook nor a comprehensive review book, and it is not a panacea for inadequate preparation.

CONSIDER *FIRST AID* YOUR ANNOTATION HUB: Annotate material from other resources, such as class notes or comprehensive textbooks, into your book. This will keep all the high-yield information you need in one place. Other tips on keeping yourself organized:

- For best results, use fine-tipped ballpoint pens (eg, BIC Pro+, Uni-Ball Jetstream Sports, Pilot Drawing Pen, Zebra F-301). If you like gel pens, try Pentel Slicci, and for markers that dry almost immediately, consider Staedtler Triplus Fineliner, Pilot Drawing Pen, and Sharpies.
- Consider using pens with different colors of ink to indicate different sources of information (eg, blue for USMLE-Rx Step 1 Qmax, green for UWorld Step 1 Qbank).
- Choose highlighters that are bright and dry quickly to minimize smudging and bleeding through the page (eg, Tombow Kei Coat, Sharpie Gel).
- Many students de-spine their book and get it 3-hole-punched. This will allow you to insert materials from other sources, such as course syllabi.

INTEGRATE STUDY WITH CASES, FLASH CARDS, AND QUESTIONS: To broaden your learning strategy, consider integrating your *First Aid* study with case-based reviews (eg, *First Aid Cases for the USMLE Step 1*), flash cards (eg, First Aid Flash Facts), and practice questions (eg, the USMLE-Rx Step 1 Qmax). Read the chapter in the book, then test your comprehension by using cases, flash cards, and questions that cover the same topics. Maintain access to more comprehensive resources (eg, *First Aid for the Basic Sciences: General Principles* and *Organ Systems* and First Aid Express videos) for deeper review as needed.

PRIME YOUR MEMORY: Return to your annotated Sections II and III several days before taking the USMLE Step 1. The book can serve as a useful way of retaining key associations and keeping high-yield facts fresh in your memory just prior to the exam. The Rapid Review section includes high-yield topics to help guide your studying.

CONTRIBUTE TO FIRST AID: Reviewing the book immediately after your exam can help us improve the next edition. Decide what was truly high and low yield and send us your comments. Feel free to send us scanned images from your annotated *First Aid* book as additional support. Of course, always remember that **all examinees are under agreement with the NBME to not disclose the specific details of copyrighted test material.**

Selected USMLE Laboratory Values

* = Included in the Biochemical Profile (SMA-12)

Blood, Plasma, Serum	Reference Range	SI Reference Intervals
*Alanine aminotransferase (ALT, GPT at 30°C)	8–20 U/L	8–20 U/L
Amylase, serum	25–125 U/L	25–125 U/L
*Aspartate aminotransferase (AST, GOT at 30°C)	8–20 U/L	8–20 U/L
Bilirubin, serum (adult)		
Total // Direct	0.1–1.0 mg/dL // 0.0–0.3 mg/dL	2–17 µmol/L // 0–5 µmol/L
*Calcium, serum (Total)	8.4–10.2 mg/dL	2.1–2.8 mmol/L
*Cholesterol, serum (Total)	< 200 mg/dL	< 5.2 mmol/L
*Creatinine, serum (Total)	0.6–1.2 mg/dL	53–106 µmol/L
Electrolytes, serum		
Sodium	136–145 mEq/L	136–145 mmol/L
Chloride	95–105 mEq/L	95–105 mmol/L
* Potassium	3.5–5.0 mEq/L	3.5–5.0 mmol/L
Bicarbonate	22–28 mEq/L	22–28 mmol/L
Magnesium	1.5 mEq/L	0.75–1.0 mmol/L
Gases, arterial blood (room air)		
P_{O_2}	75–105 mm Hg	10.0–14.0 kPa
P_{CO_2}	33–44 mm Hg	4.4–5.9 kPa
pH	7.35–7.45	$[H^+]$ 36–44 nmol/L
*Glucose, serum	Fasting: 70–110 mg/dL 2-h postprandial: < 120 mg/dL	3.8–6.1 mmol/L < 6.6 mmol/L
Growth hormone – arginine stimulation	Fasting: < 5 ng/mL provocative stimuli: > 7 ng/mL	< 5 µg/L > 7 µg/L
Osmolality, serum	275–295 mOsm/kg	275–295 mOsm/kg
*Phosphatase (alkaline), serum (p-NPP at 30°C)	20–70 U/L	20–70 U/L
*Phosphorus (inorganic), serum	3.0–4.5 mg/dL	1.0–1.5 mmol/L
Prolactin, serum (hPRL)	< 20 ng/mL	< 20 µg/L
*Proteins, serum		
Total (recumbent)	6.0–7.8 g/dL	60–78 g/L
Albumin	3.5–5.5 g/dL	35–55 g/L
Globulins	2.3–3.5 g/dL	23–35 g/L
*Urea nitrogen, serum (BUN)	7–18 mg/dL	1.2–3.0 mmol/L
*Uric acid, serum	3.0–8.2 mg/dL	0.18–0.48 mmol/L

(continues)

Cerebrospinal Fluid	Reference Range	SI Reference Intervals
Glucose	40–70 mg/dL	2.2–3.9 mmol/L
Hematologic		
Erythrocyte count	Male: 4.3–5.9 million/mm^3 Female: 3.5–5.5 million/mm^3	$4.3–5.9 \times 10^{12}$/L $3.5–5.5 \times 10^{12}$/L
Erythrocyte sedimentation rate (Westergen)	Male: 0–15 mm/h Female: 0–20 mm/h	0–15 mm/h 0–20 mm/h
Hematocrit	Male: 41–53% Female: 36–46%	0.41–0.53 0.36–0.46
Hemoglobin, blood	Male: 13.5–17.5 g/dL Female: 12.0–16.0 g/dL	2.09–2.71 mmol/L 1.86–2.48 mmol/L
Hemoglobin, plasma	1–4 mg/dL	0.16–0.62 µmol/L
Leukocyte count and differential		
Leukocyte count	4500–11,000/mm^3	$4.5–11.0 \times 10^9$/L
Segmented neutrophils	54–62%	0.54–0.62
Band forms	3–5%	0.03–0.05
Eosinophils	1–3%	0.01–0.03
Basophils	0–0.75%	0–0.0075
Lymphocytes	25–33%	0.25–0.33
Monocytes	3–7%	0.03–0.07
Mean corpuscular hemoglobin	25.4–34.6 pg/cell	0.39–0.54 fmol/cell
Mean corpuscular volume	80–100 µm^3	80–100 fL
Partial thromboplastin time (activated)	25–40 seconds	25–40 seconds
Platelet count	150,000–400,000/mm^3	$150–400 \times 10^9$/L
Prothrombin time	11–15 seconds	11–15 seconds
Reticulocyte count	0.5–1.5% of red cells	0.005–0.015
Sweat		
Chloride	0–35 mmol/L	0–35 mmol/L
Urine		
Proteins, total	< 150 mg/24 h	< 0.15 g/24 h

First Aid Checklist for the USMLE Step 1

This is an example of how you might use the information in Section I to prepare for the USMLE Step 1. Refer to corresponding topics in Section I for more details.

Years Prior

☐ Select top-rated review resources as study guides for first-year medical school courses.
☐ Ask for advice from those who have recently taken the USMLE Step 1.

Months Prior

☐ Review computer test format and registration information.
☐ Register six months in advance. Carefully verify name and address printed on scheduling permit. Call Prometric or go online for test date ASAP.
☐ Define goals for the USMLE Step 1 (eg, comfortably pass, beat the mean, ace the test).
☐ Set up a realistic timeline for study. Cover less crammable subjects first. Review subject-by-subject emphasis and clinical vignette format.
☐ Simulate the USMLE Step 1 to pinpoint strengths and weaknesses in knowledge and test-taking skills.
☐ Evaluate and choose study methods and materials (eg, review books, question banks).

Weeks Prior

☐ Simulate the USMLE Step 1 again. Assess how close you are to your goal.
☐ Pinpoint remaining weaknesses. Stay healthy (exercise, sleep).
☐ Verify information on admission ticket (eg, location, date).

One Week Prior

☐ Remember comfort measures (loose clothing, earplugs, etc).
☐ Work out test site logistics such as location, transportation, parking, and lunch.
☐ Call Prometric and confirm your exam appointment.

One Day Prior

☐ Relax.
☐ Lightly review short-term material if necessary. Skim high-yield facts.
☐ Get a good night's sleep.
☐ Make sure the name printed on your photo ID appears EXACTLY the same as the name printed on your scheduling permit.

Day of Exam

☐ Relax. Eat breakfast. Minimize bathroom breaks during the exam by avoiding excessive morning caffeine.
☐ Analyze and make adjustments in test-taking technique. You are allowed to review notes/study material during breaks on exam day.

After the Exam

☐ Celebrate, regardless.
☐ Send feedback to us on our website at **www.firstaidteam.com.**

SECTION I

Guide to Efficient Exam Preparation

"A mind of moderate capacity which closely pursues one study must infallibly arrive at great proficiency in that study."

—Mary Shelley, *Frankenstein*

"Finally, from so little sleeping and so much reading, his brain dried up and he went completely out of his mind."

—Miguel de Cervantes Saavedra, *Don Quixote*

"Sometimes the questions are complicated and the answers are simple."

—Dr. Seuss

"He who knows all the answers has not been asked all the questions."

—Confucius

"It's what you learn after you know it all that counts."

—John Wooden

"A goal without a plan is just a wish."

—Antoine de Saint-Exupéry

- Introduction 2
- USMLE Step 1—The Basics 2
- Defining Your Goal 12
- Excelling in the Preclinical Years 13
- Timeline for Study 14
- Study Materials 18
- Test-Taking Strategies 20
- Clinical Vignette Strategies 21
- If You Think You Failed 22
- Testing Agencies 22
- References 23

INTRODUCTION

Relax.

This section is intended to make your exam preparation easier, not harder. Our goal is to reduce your level of anxiety and help you make the most of your efforts by helping you understand more about the United States Medical Licensing Examination, Step 1 (USMLE Step 1). As a medical student, you are no doubt familiar with taking standardized examinations and quickly absorbing large amounts of material. When you first confront the USMLE Step 1, however, you may find it all too easy to become sidetracked from your goal of studying with maximal effectiveness. Common mistakes that students make when studying for Step 1 include the following:

- Starting to study (including *First Aid*) too late
- Starting to study intensely too early and burning out
- Starting to prepare for boards before creating a knowledge foundation
- Using inefficient or inappropriate study methods
- Buying the wrong resources or buying too many resources
- Buying only one publisher's review series for all subjects
- Not using practice examinations to maximum benefit
- Not understanding how scoring is performed or what the score means
- Not using review books along with your classes
- Not analyzing and improving your test-taking strategies
- Getting bogged down by reviewing difficult topics excessively
- Studying material that is rarely tested on the USMLE Step 1
- Failing to master certain high-yield subjects owing to overconfidence
- Using *First Aid* as your sole study resource
- Trying to prepare for it all alone

In this section, we offer advice to help you avoid these pitfalls and be more productive in your studies.

The test at a glance:

- *8-hour exam*
- *Total of 280 multiple choice items*
- *7 test blocks (60 min/block)*
- *Up to 40 test items per block*
- *45 minutes of break time, plus another 15 if you skip the tutorial*

USMLE STEP 1—THE BASICS

The USMLE Step 1 is the first of three examinations that you must pass in order to become a licensed physician in the United States. The USMLE is a joint endeavor of the National Board of Medical Examiners (NBME) and the Federation of State Medical Boards (FSMB). The USMLE serves as the single examination system for US medical students and international medical graduates (IMGs) seeking medical licensure in the United States.

The Step 1 exam includes test items drawn from the following content areas[1]:

DISCIPLINE

Aging
Anatomy
Behavioral Sciences
Biochemistry
Biostatistics and Epidemiology
Genetics
Immunology
Microbiology
Molecular and Cell Biology
Nutrition
Pathology
Pharmacology
Physiology

ORGAN SYSTEM

Behavioral Health & Nervous Systems/Special Senses
Biostatistics & Epidemiology/Population Health/Social Sciences
Blood & Lymphoreticular System
Cardiovascular System
Endocrine System
Gastrointestinal System
General Principles of Foundational Science
Immune System
Multisystem Processes & Disorders
Musculoskeletal, Skin, & Subcutaneous Tissue
Renal/Urinary System
Reproductive System
Respiratory System

How Is the Computer-Based Test (CBT) Structured?

The CBT Step 1 exam consists of one "optional" tutorial/simulation block and seven "real" question blocks of up to 40 questions per block with no more than 280 questions in total, timed at 60 minutes per block. A short 11-question survey follows the last question block. The computer begins the survey with a prompt to proceed to the next block of questions.

Once an examinee finishes a particular question block on the CBT, he or she must click on a screen icon to continue to the next block. Examinees **cannot** go back and change their answers to questions from any previously completed block. However, changing answers is allowed **within** a block of questions as long as the block has not been ended and if time permits.

What Is the CBT Like?

Given the unique environment of the CBT, it's important that you become familiar ahead of time with what your test-day conditions will be like. In fact, you can easily add up to 15 minutes to your break time! This is because the 15-minute tutorial offered on exam day may be skipped if you are already familiar with the exam procedures and the testing interface. The 15 minutes is then added to your allotted break time of 45 minutes for a total of 1 hour of potential break time. You can download the tutorial from the USMLE website and do it before test day. This tutorial interface is very similar to the one you will use in the exam; learn it now and you can skip taking it during the exam, giving you up to 15 extra minutes of break time. You can also gain experience

- *If you know the format, you can skip the tutorial and add up to 15 minutes to your break time!*

with the CBT format by taking the 120 practice questions (3 blocks with 40 questions each) available online or by signing up for a practice session at a test center.

For security reasons, examinees are not allowed to bring any personal electronic equipment into the testing area. This includes both digital and analog watches, iPods, tablets, calculators, cell phones, and electronic paging devices. Examinees are also prohibited from carrying in their books, notes, pens/pencils, and scratch paper. Food and beverages are also prohibited in the testing area. The testing centers are monitored by audio and video surveillance equipment. However, most testing centers allot each examinee a small locker outside the testing area in which he or she can store snacks, beverages, and personal items.

Keyboard shortcuts:
- *A, B, etc—letter choices*
- *Enter or spacebar—move to next question*
- *Esc—exit pop-up Lab and Exhibit windows*
- *Alt-T—countdown timers for current session and overall test*

The typical question screen in the CBT consists of a question followed by a number of choices on which an examinee can click, together with several navigational buttons on the top of the screen. There is a countdown timer on the lower left corner of the screen as well. There is also a button that allows the examinee to mark a question for review. If a given question happens to be longer than the screen (which occurs very rarely), a scroll bar will appear on the right, allowing the examinee to see the rest of the question. Regardless of whether the examinee clicks on an answer choice or leaves it blank, he or she must click the "Next" button to advance to the next question.

Heart sounds are tested via media questions. Make sure you know how different heart diseases sound on auscultation.

Be sure to test your headphones during the tutorial.

The USMLE features a small number of media clips in the form of audio and/or video. There may even be a question with a multimedia heart sound simulation. In these questions, a digital image of a torso appears on the screen, and the examinee directs a digital stethoscope to various auscultation points to listen for heart and breath sounds. The USMLE orientation materials include several practice questions in these formats. During the exam tutorial, examinees are given an opportunity to ensure that both the audio headphones and the volume are functioning properly. If you are already familiar with the tutorial and planning on skipping it, first skip ahead to the section where you can test your headphones. After you are sure the headphones are working properly, proceed to the exam.

Familiarize yourself with the commonly tested lab values.

The examinee can call up a window displaying normal laboratory values. In order to do so, he or she must click the "Lab" icon on the top part of the screen. Afterward, the examinee will have the option to choose between "Blood," "Cerebrospinal," "Hematologic," or "Sweat and Urine." The normal-values screen may obscure the question if it is expanded. The examinee may have to scroll down to search for the needed lab values. You might want to memorize some common lab values so you spend less time on questions that require you to analyze these.

Illustrations on the test include:
- *Gross specimen photos*
- *Histology slides*
- *Medical imaging (eg, x-ray, CT, MRI)*
- *Electron micrographs*
- *Line drawings*

The CBT interface provides a running list of questions on the left part of the screen at all times. The software also permits examinees to highlight or cross out information by using their mouse. There is a "Notes" icon on the top part of the screen that allows students to write notes to themselves for review at a later time. Finally, the USMLE has recently added new functionality including text magnification and reverse color (white text on black background). Being familiar with these features can save time and may help you better view and organize the information you need to answer a question.

▸ *Ctrl-Alt-Delete are the keys of death during the exam. Don't touch them at the same time!*

For those who feel they might benefit, the USMLE offers an opportunity to take a simulated test, or "CBT Practice Session" at a Prometric center. Students are eligible to register for this three-and-one-half-hour practice session after they have received their scheduling permit.

▸ *You can take a shortened CBT practice test at a Prometric center.*

The same USMLE Step 1 sample test items (120 questions) available on the USMLE website, www.usmle.org, are used at these sessions. **No new items will be presented.** The session is divided into a short tutorial and three 1-hour blocks of ~40 test items each at a cost of $75, if your testing region is in the United States or Canada. Students receive a printed percent-correct score after completing the session. **No explanations of questions are provided.**

You may register for a practice session online at www.usmle.org. A separate scheduling permit is issued for the practice session. Students should allow two weeks for receipt of this permit.

How Do I Register to Take the Exam?

▸ *The Prometric Web site will display a calendar with open test dates.*

Prometric test centers offer Step 1 on a year-round basis, except for the first two weeks in January and major holidays. The exam is given every day except Sunday at most centers. Some schools administer the exam on their own campuses. Check with the test center you want to use before making your exam plans.

US students can apply to take Step 1 at the NBME website. This application allows you to select one of 12 overlapping three-month blocks in which to be tested (eg, April–May–June, June–July–August). Choose your three-month eligibility period wisely. If you need to reschedule outside your initial three-month period, you can request a one-time extension of eligibility for the next contiguous three-month period, and pay a rescheduling fee. The application also includes a photo ID form that must be certified by an official at your medical school to verify your enrollment. After the NBME processes your application, it will send you a scheduling permit.

The scheduling permit you receive from the NBME will contain your USMLE identification number, the eligibility period in which you may take the exam, and two additional numbers. The first of these is known as your "scheduling number." You must have this number in order to make your exam appointment with Prometric. The second number is known as the "candidate identification number," or CIN. Examinees must enter their CINs at the Prometric workstation in order to access their exams. However, you will not be allowed to bring your permit into the exam and will be asked to copy your CIN onto your scratch paper. Prometric has no access to the codes. **Do not lose your permit!** You will not be allowed to take the exam unless you present this permit along with an unexpired, government-issued photo ID that includes your signature (such as a driver's license or passport). Make sure the name on your photo ID exactly matches the name that appears on your scheduling permit.

- *The confirmation emails that Prometric and NBME send are not the same as the scheduling permit.*

Once you receive your scheduling permit, you may access the Prometric website or call Prometric's toll-free number to arrange a time to take the exam. You may contact Prometric two weeks before the test date if you want to confirm identification requirements. Although requests for taking the exam may be completed more than six months before the test date, examinees will not receive their scheduling permits earlier than six months before the eligibility period. The eligibility period is the three-month period you have chosen to take the exam. Most medical students choose the April–June or June–August period. Because exams are scheduled on a "first-come, first-served" basis, it is recommended that you contact Prometric as soon as you receive your permit. After you've scheduled your exam, it's a good idea to confirm your exam appointment with Prometric at least one week before your test date. Prometric will provide appointment confirmation on a print-out and by email. Be sure to read the *2017 USMLE Bulletin of Information* for further details.

- *Test scheduling is done on a "first-come, first-served" basis. It's important to call and schedule an exam date as soon as you receive your scheduling permit.*

What If I Need to Reschedule the Exam?

You can change your test date and/or center by contacting Prometric at 1-800-MED-EXAM (1-800-633-3926) or www.prometric.com. Make sure to have your CIN when rescheduling. If you are rescheduling by phone, you must speak with a Prometric representative; leaving a voicemail message will not suffice. To avoid a rescheduling fee, you will need to request a change at least 31 calendar days before your appointment. Please note that your rescheduled test date must fall within your assigned three-month eligibility period.

- *Register six months in advance for seating and scheduling preference.*

When Should I Register for the Exam?

You should plan to register as far in advance as possible ahead of your desired test date (eg, six months), but, depending on your particular test center, new dates and times may open closer to the date. Scheduling early will guarantee that you will get either your test center of choice or one within a 50-mile radius of your first choice. For most US medical students, the desired testing window is in June, since most medical school curricula for the second year end in May or June. Thus, US medical students should plan to register before January in anticipation of a June test date. The timing of the exam is more flexible for IMGs, as it is related only to when they finish exam preparation. Talk with upperclassmen who have already taken the test so you have real-life experience from students who went through a similar curriculum, then formulate your own strategy.

Where Can I Take the Exam?

Your testing location is arranged with Prometric when you call for your test date (after you receive your scheduling permit). For a list of Prometric locations nearest you, visit www.prometric.com.

How Long Will I Have to Wait Before I Get My Scores?

The USMLE reports scores in three to four weeks, unless there are delays in score processing. Examinees will be notified via email when their scores are available. By following the online instructions, examinees will be able to view, download, and print their score report. Additional information about score timetables and accessibility is available on the official USMLE website.

What About Time?

Time is of special interest on the CBT exam. Here's a breakdown of the exam schedule:

▸ *Gain extra break time by skipping the tutorial or finishing a block early.*

15 minutes	Tutorial (skip if familiar with test format and features)
7 hours	Seven 60-minute question blocks
45 minutes	Break time (includes time for lunch)

The computer will keep track of how much time has elapsed on the exam. However, the computer will show you only how much time you have remaining in a given block. Therefore, it is up to you to determine if you are pacing yourself properly (at a rate of approximately one question per 90 seconds).

The computer will not warn you if you are spending more than your allotted time for a break. You should therefore budget your time so that you can take a short break when you need one and have time to eat. You must be especially careful not to spend too much time in between blocks (you should keep track of how much time elapses from the time you finish a block of questions to the time you start the next block). After you finish one question block, you'll need to click to proceed to the next block of questions. If you do not click within 30 seconds, you will automatically be entered into a break period.

Break time for the day is 45 minutes, but you are not required to use all of it, nor are you required to use any of it. You can gain extra break time (but not extra time for the question blocks) by skipping the tutorial or by finishing a block ahead of the allotted time. Any time remaining on the clock when you finish a block gets added to your remaining break time. Once a new question block has been started, you may not take a break until you have reached the end of that block. If you do so, this will be recorded as an "unauthorized break" and will be reported on your final score report.

▸ *Be careful to watch the clock on your break time.*

Finally, be aware that it may take a few minutes of your break time to "check out" of the secure resting room and then "check in" again to resume testing, so plan accordingly. The "check-in" process may include fingerprints, pocket checks, and metal detector scanning. Some students recommend pocketless clothing on exam day to streamline the process.

If I Freak Out and Leave, What Happens to My Score?

Your scheduling permit shows a CIN that you will need to enter to start your exam. Entering the CIN is the same as breaking the seal on a test book, and you are considered to have started the exam when you do so. However, no score will be reported if you do not complete the exam. In fact, if you leave at any time from the start of the test to the last block, no score will be reported. The fact that you started but did not complete the exam, however, will appear on your USMLE score transcript. Even though a score is not posted for incomplete tests, examinees may still get an option to request that their scores be calculated and reported if they desire; unanswered questions will be scored as incorrect.

The exam ends when all question blocks have been completed or when their time has expired. As you leave the testing center, you will receive a printed test-completion notice to document your completion of the exam. To receive an official score, you must finish the entire exam.

What Types of Questions Are Asked?

- *Nearly three fourths of Step 1 questions begin with a description of a patient.*

All questions on the exam are **one-best-answer multiple choice items.** Sequential item sets have been removed. Most questions consist of a clinical scenario or a direct question followed by a list of five or more options. You are required to select the single best answer among the options given. There are no "except," "not," or matching questions on the exam. A number of options may be partially correct, in which case you must select the option that best answers the question or completes the statement. Additionally, keep in mind that experimental questions may appear on the exam, which do not affect your score.

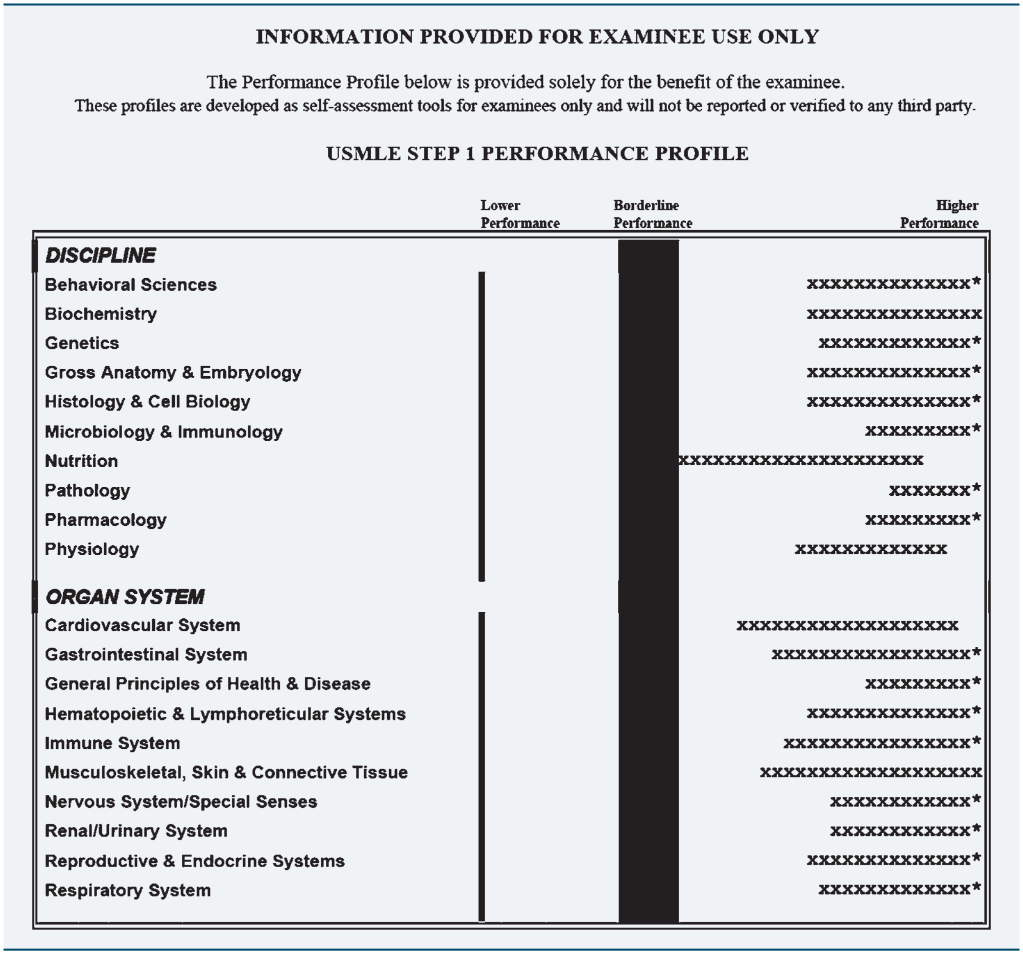
How Is the Test Scored?

Each Step 1 examinee receives an electronic score report that includes the examinee's pass/fail status, a three-digit test score, and a graphic depiction of the examinee's performance by discipline and organ system or subject area. The actual organ system profiles reported may depend on the statistical characteristics of a given administration of the examination.

The USMLE score report is divided into two sections: performance by discipline and performance by organ system. Each of the questions (minus experimental questions) is tagged according to any or all relevant content areas. Your performance in each discipline and each organ system is represented by a line of X's, where the width of the line is related to the confidence interval for your performance, which is often a direct consequence of the total number of questions for each discipline/system. If any lines have an asterisk (*) at the far right, this means your performance was exemplary in that area—not necessarily representing a perfect score, but often close to it (see Figure 1).

The NBME provides a three-digit test score based on the total number of items answered correctly on the examination (see Figure 2). Your three-digit score will be qualified by the mean and standard deviation of US and Canadian

FIGURE 1. Sample USMLE Step 1 Performance Profile



INFORMATION PROVIDED FOR EXAMINEE USE ONLY

The Performance Profile below is provided solely for the benefit of the examinee.
These profiles are developed as self-assessment tools for examinees only and will not be reported or verified to any third party.

USMLE STEP 1 PERFORMANCE PROFILE

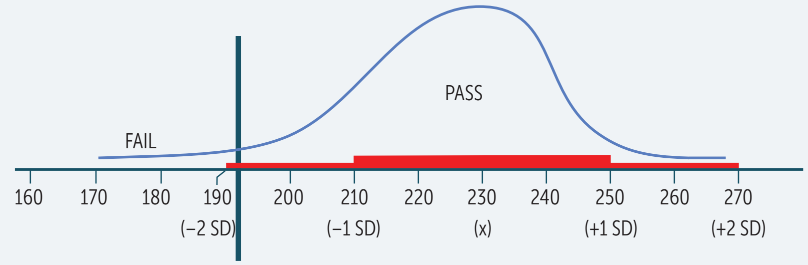
	Lower Performance	Borderline Performance	Higher Performance
DISCIPLINE			
Behavioral Sciences			xxxxxxxxxxxxxx*
Biochemistry			xxxxxxxxxxxxxxx
Genetics			xxxxxxxxxxxxx*
Gross Anatomy & Embryology			xxxxxxxxxxxxxx*
Histology & Cell Biology			xxxxxxxxxxxxxx*
Microbiology & Immunology			xxxxxxxxx*
Nutrition			xxxxxxxxxxxxxxxxxxxxx
Pathology			xxxxxxx*
Pharmacology			xxxxxxxxx*
Physiology			xxxxxxxxxxxxx
ORGAN SYSTEM			
Cardiovascular System			xxxxxxxxxxxxxxxxxxx
Gastrointestinal System			xxxxxxxxxxxxxxxxx*
General Principles of Health & Disease			xxxxxxxxx*
Hematopoietic & Lymphoreticular Systems			xxxxxxxxxxxxxx*
Immune System			xxxxxxxxxxxxxxxx*
Musculoskeletal, Skin & Connective Tissue			xxxxxxxxxxxxxxxxxxx
Nervous System/Special Senses			xxxxxxxxxxxx*
Renal/Urinary System			xxxxxxxxxxxx*
Reproductive & Endocrine Systems			xxxxxxxxxxxxxx*
Respiratory System			xxxxxxxxxxxxx*

medical school first-time examinees. The translation from the lines of X's and number of asterisks you receive on your report to the three-digit score is unclear, but higher three-digit scores are associated with more asterisks.

Since some questions may be experimental and are not counted, it is possible to get different scores for the same number of correct answers. In 2015, the mean score was 229 with a standard deviation of 20.

▶ *The mean Step 1 score for US medical students continues to rise, from 200 in 1991 to 229 in 2015.*

FIGURE 2. Scoring Scale for the USMLE Step 1.



A score of **192** or higher is required to pass Step 1. The NBME does not report the minimum number of correct responses needed to pass, but estimates that it is roughly 60–70%. The NBME may adjust the minimum passing score in the future, so please check the USMLE website or www.firstaidteam.com for updates.

According to the USMLE, medical schools receive a listing of total scores and pass/fail results plus group summaries by discipline and organ system. Students can withhold their scores from their medical school if they wish. Official USMLE transcripts, which can be sent on request to residency programs, include only total scores, not performance profiles.

Consult the USMLE website or your medical school for the most current and accurate information regarding the examination.

What Does My Score Mean?

The most important point with the Step 1 score is passing versus failing. Passing essentially means, "Hey, you're on your way to becoming a fully licensed doc." As Table 1 shows, the majority of students pass the exam, so remember, we told you to relax.

Beyond that, the main point of having a quantitative score is to give you a sense of how well you've done on the exam and to help schools and residencies rank their students and applicants, respectively.

Official NBME/USMLE Resources

The NBME offers a Comprehensive Basic Science Examination (CBSE) for practice that is a shorter version of the Step 1. The CBSE contains four blocks

TABLE 1. Passing Rates for the 2014–2015 USMLE Step 1.[2]

	2014		2015	
	No. Tested	% Passing	No. Tested	% Passing
Allopathic 1st takers	19,582	96%	20,213	96%
Repeaters	812	68%	898	68%
Allopathic total	20,394	95%	21,111	94%
Osteopathic 1st takers	2,810	93%	3,185	93%
Repeaters	36	69%	37	65%
Osteopathic total	2,846	93%	3,222	93%
Total US/Canadian	**23,240**	**95%**	**24,333**	**94%**
IMG 1st takers	15,149	78%	15,030	78%
Repeaters	2,889	38%	2,719	38%
IMG total	18,038	72%	17,749	72%
Total Step 1 examinees	**41,278**	**85%**	**42,082**	**85%**

of 50 questions each and covers material that is typically learned during the basic science years. Scores range from 45 to 95 and correlate with a Step 1 equivalent (see Table 2). The standard error of measurement is approximately 3 points, meaning a score of 80 would estimate the student's proficiency is somewhere between 77 and 83. In other words, the actual Step 1 score could be predicted to be between 218 and 232. Of course, these values do not correlate exactly, and they do not reflect different test preparation methods. Many schools use this test to gauge whether a student is expected to pass Step 1. If this test is offered by your school, it is usually conducted at the end of regular didactic time before any dedicated Step 1 preparation. If you do not encounter the CBSE before your dedicated study time, you need not worry about taking it. Use the information to help set realistic goals and timetables for your success.

TABLE 2. CBSE to USMLE Score Prediction.

CBSE Score	Step 1 Equivalent
≥ 94	≥ 260
92	255
90	250
88	245
86	240
84	235
82	230
80	225
78	220
76	215
74	210
72	205
70	200
68	195
66	190
64	185
62	180
60	175
58	170
56	165
54	160
52	155
50	150
48	145
46	140
≤ 44	≤ 135

The NBME also offers six forms of Comprehensive Basic Science Self-Assessment (CBSSA). Students who prepared for the exam using this web-based tool reported that they found the format and content highly indicative of questions tested on the actual exam. In addition, the CBSSA is a fair predictor of USMLE performance (see Table 3). The test interface, however, does not match the actual USMLE test interface, so practicing with these forms alone is not advised.

The CBSSA exists in two formats: standard-paced and self-paced, both of which consist of four sections of 50 questions each (for a total of 200 multiple choice items). The standard-paced format allows the user up to 65 minutes to complete each section, reflecting time limits similar to the actual exam. By contrast, the self-paced format places a 4:20 time limit on answering all multiple choice questions. Every few years, a new form is released and an older one is retired, reflecting changes in exam content. Therefore, the newer exams tend to be more similar to the actual Step 1, and scores from these exams tend to provide a better estimation of exam day performance.

▸ *Practice questions may be easier than the actual exam.*

Keep in mind that this bank of questions is available only on the web. The NBME requires that users log on, register, and start the test within 30 days of registration. Once the assessment has begun, users are required to complete the sections within 20 days. Following completion of the questions, the CBSSA provides a performance profile indicating the user's relative strengths and weaknesses, much like the report profile for the USMLE Step 1 exam. The profile is scaled with an average score of 500 and a standard deviation of 100. Please note that the CBSSAs do not list the correct answers to the questions at the end of the session. However, forms can be purchased with an extended feedback option; these tests show you which questions you answered incorrectly, but do not show you the correct answer or explain why your choice was wrong. Feedback from the self-assessment takes the form of a performance profile and nothing more. The NBME charges $50 for assessments without feedback and $60 for assessments with expanded feedback. The fees are payable by credit card or money order. For more information regarding the CBSE and the CBSSA, visit the NBME's website at www.nbme.org.

The NBME scoring system is weighted for each assessment exam. While some exams seem more difficult than others, the score reported takes into account these inter-test differences when predicting Step 1 performance. Also, while many students report seeing Step 1 questions "word-for-word" out of the assessments, the NBME makes special note that no live USMLE questions are shown on any NBME assessment.

Lastly, the International Foundations of Medicine (IFOM) offers a Basic Science Examination (BSE) practice exam at participating Prometric test centers for $200. Students may also take the self-assessment test online for $35 through the NBME's website. The IFOM BSE is intended to determine an examinee's relative areas of strength and weakness in general areas of basic science—not to predict performance on the USMLE Step 1 exam—and the content covered by the two examinations is somewhat different. However, because there is substantial overlap in content coverage and many IFOM items were previously used on the USMLE Step 1, it is possible to roughly project IFOM performance onto the USMLE Step 1 score scale. More information is available at http://www.nbme.org/ifom/.

TABLE 3. CBSSA to USMLE Score Prediction.

CBSSA Score	Approximate USMLE Step 1 Score
150	153
200	164
250	175
300	185
350	196
400	207
450	217
500	228
550	239
600	249
650	260
700	271
750	281
800	292

DEFINING YOUR GOAL

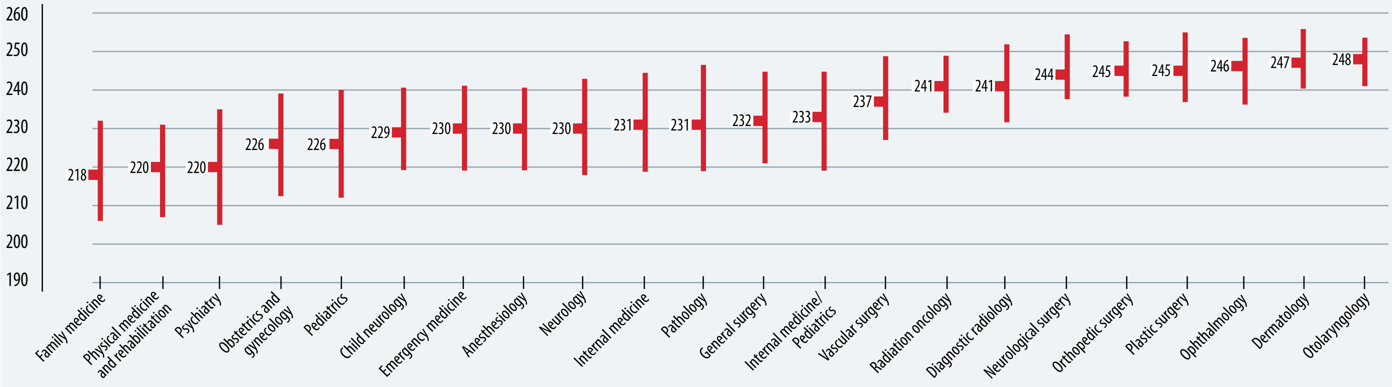
It is useful to define your own personal performance goal when approaching the USMLE Step 1. Your style and intensity of preparation can then be matched to your goal. Furthermore, your goal may depend on your school's requirements, your specialty choice, your grades to date, and your personal assessment of the test's importance. Do your best to define your goals early so that you can prepare accordingly.

Some competitive residency programs place more weight on Step 1 scores when choosing candidates to interview.

The value of the USMLE Step 1 score in selecting residency applicants remains controversial, and some have called for less emphasis to be placed on the score when selecting or screening applicants.[3] For the time being, however, it continues to be an important part of the residency application, and it is not uncommon for some specialties to implement filters that screen out applicants who score below a certain cutoff. This is more likely to be seen in competitive specialties (eg orthopedic surgery, ophthalmology, dermatology, otolaryngology). Independent of your career goals, you can maximize your future options by doing your best to obtain the highest score possible (see Figure 3). At the same time, your Step 1 score is only one of a number of factors that are assessed when you apply for residency. In fact, many residency programs value other criteria such as letters of recommendation, third-year clerkship grades, honors, and research experience more than a high score on Step 1. Fourth-year medical students who have recently completed the residency application process can be a valuable resource in this regard.

Fourth-year medical students have the best feel for how Step 1 scores factor into the residency application process.

FIGURE 3. Median USMLE Step 1 Score by Specialty for Matched US Seniors.[a,b]



[a] Vertical lines show interquartile range.

[b] Data from National Resident Matching Program. Charting outcomes in the match. http://www.nrmp.org/wp-content/uploads/2014/09/Charting-Outcomes-2014-Final.pdf. Published August 2014. Accessed September 1, 2016. Ophthalmology data from SF Match Residency and Fellowship Matching Services. Ophthalmology residency. https://www.sfmatch.org/SpecialtyInsideAll.aspx?id=6&typ=2&name=Ophthalmology. Accessed September 1, 2016.

▶ EXCELLING IN THE PRECLINICAL YEARS

Many students feel overwhelmed during the first few weeks of medical school and struggle to find a workable system. Strategies that worked during your undergraduate years may or may not work as you prepare for the USMLE Step 1. Below are three study methods to use during the preclinical years and their effectiveness for Step 1 preparation. Regardless of your choice, the foundation of knowledge you build during your basic science years is the most important resource for success on the USMLE Step 1.

Read, Highlight, Reread

This is the traditional way of learning and involves reading through material in an attempt to directly memorize it. Common sources include lecture notes and textbooks. Students read through these sources multiple times and use methods such as highlighting to emphasize important points. Because this method is passive and does not use active techniques, such as information retrieval (eg, applying learned material while answering a practice question), it tends to be of minimal value for Step 1 preparation. Students do not learn how to actively recall learned information and apply it to difficult Step 1 questions. As a result, it has largely been abandoned in favor of more active techniques.[4]

Flash Cards

There is no shortage of flash card applications, from make-your-own cards to purchasable premade decks. Self-made flash cards, if done correctly, offer the ability to objectively test necessary facts. Written in an open-ended format and coupled with spaced repetition, they train both recognition and recall. Spaced repetition and active recall have been consistently shown to improve long-term retention of knowledge. Studies have also linked spaced repetition learning

▶ *Watch out for flash card overload!*

with flash cards to higher exam scores.[5,6,7] Apps (eg, Anki, First Aid Flash Facts) exist for various smartphones and tablets, so the flash cards are always accessible. However, the ease of quickly creating digital cards and sharing can lead to flash card overload (it is unsustainable to make 50 flash cards per lecture!). Even at a modest pace, the thousands upon thousands of cards are too overwhelming for Step 1 preparation. Unless you have specified high-yield cards (and checked the content with high-yield resources), stick to premade cards by reputable sources that curate the vast amount of knowledge for you.

Tables and Summaries

This is a more active (and time intensive) form of learning. It consists of integrating the pertinent information from resources on each subject into tables and summaries that cut across topics within the same category. A table is a graphical means of organizing information succinctly. A summary is actively explaining the synthesized content in a manner that is understandable to the learner. The key is to synthesize the sequentially presented material. While many review sources offer this material in various styles and formats, your own class notes may in fact be concise enough to use as an adjunct for Step 1 preparation, and they have the added benefit of being organized to your liking.

▶ TIMELINE FOR STUDY

Before Starting

Your preparation for the USMLE Step 1 should begin when you enter medical school. Organize and commit to studying from the beginning so that when the time comes to prepare for the USMLE, you will be ready with a strong foundation.

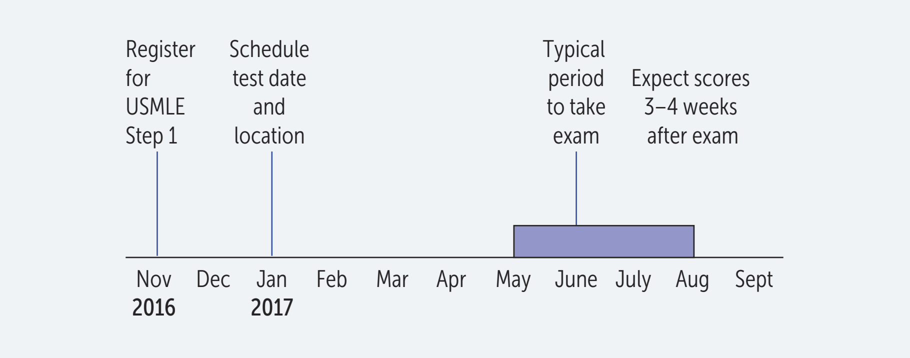
Make a Schedule

▶ Customize your schedule. Tackle your weakest section first.

After you have defined your goals, map out a study schedule that is consistent with your objectives, your vacation time, the difficulty of your ongoing coursework, and your family and social commitments (see Figure 4). Determine whether you want to spread out your study time or concentrate it into 14-hour study days in the final weeks. Then factor in your own history in preparing for standardized examinations (eg, SAT, MCAT). Talk to students at your school who have recently taken Step 1. Ask them for their study schedules, especially those who have study habits and goals similar to yours.

Typically, US medical schools allot between four and eight weeks for dedicated Step 1 preparation. The time you dedicate to exam preparation will depend on your target score as well as your success in preparing yourself during the first two years of medical school. Some students reserve about a week at the

FIGURE 4. Typical Timeline for the USMLE Step 1.



end of their study period for final review; others save just a few days. When you have scheduled your exam date, do your best to adhere to it. Studies show that a later testing date does not translate into a higher score, so avoid pushing back your test date without good reason.[8]

▶ *"Crammable" subjects should be covered later and less crammable subjects earlier.*

Make your schedule realistic, and set achievable goals. Many students make the mistake of studying at a level of detail that requires too much time for a comprehensive review—reading *Gray's Anatomy* in a couple of days is not a realistic goal! Have one catch-up day per week of studying. No matter how well you stick to your schedule, unexpected events happen. But don't let yourself procrastinate because you have catch-up days; stick to your schedule as closely as possible and revise it regularly on the basis of your actual progress. Be careful not to lose focus. Beware of feelings of inadequacy when comparing study schedules and progress with your peers. **Avoid others who stress you out.** Focus on a few top-rated resources that suit your learning style—not on some obscure books your friends may pass down to you. Accept the fact that you cannot learn it all.

▶ *Avoid burnout. Maintain proper diet, exercise, and sleep habits.*

You will need time for uninterrupted and focused study. Plan your personal affairs to minimize crisis situations near the date of the test. Allot an adequate number of breaks in your study schedule to avoid burnout. Maintain a healthy lifestyle with proper diet, exercise, and sleep.

Another important aspect of your preparation is your studying environment. **Study where you have always been comfortable studying.** Be sure to include everything you need close by (review books, notes, coffee, snacks, etc). If you're the kind of person who cannot study alone, form a study group with other students taking the exam. The main point here is to create a comfortable environment with minimal distractions.

Year(s) Prior

The knowledge you gained during your first two years of medical school and even during your undergraduate years should provide the groundwork on which to base your test preparation. Student scores on NBME subject tests (commonly known as "shelf exams") have been shown to be highly correlated with subsequent Step 1 scores.[9] Moreover, undergraduate science GPAs as well as MCAT scores are strong predictors of performance on the Step 1 exam.[10]

- *Buy review books early (first year) and use while studying for courses.*

We also recommend that you buy highly rated review books early in your first year of medical school and use them as you study throughout the two years. When Step 1 comes along, these books will be familiar and personalized to the way in which you learn. It is risky and intimidating to use unfamiliar review books in the final two or three weeks preceding the exam. Some students find it helpful to personalize and annotate *First Aid* throughout the curriculum.

Months Prior

Review test dates and the application procedure. Testing for the USMLE Step 1 is done on a year-round basis. If you have disabilities or special circumstances, contact the NBME as early as possible to discuss test accommodations (see the Section I Supplement at www.firstaidteam.com/bonus).

- *Simulate the USMLE Step 1 under "real" conditions before beginning your studies.*

Use this time to finalize your ideal schedule. Consider upcoming breaks and whether you want to relax or study. Work backward from your test date to make sure you finish at least one question bank. Also add time to redo missed or flagged questions (which may be half the bank). This is the time to build a structured plan with enough flexibility for the realities of life.

Begin doing blocks of questions from reputable question banks under "real" conditions. Don't use tutor mode until you're sure you can finish blocks in the allotted time. It is important to continue balancing success in your normal studies with the Step 1 test preparation process.

Weeks Prior (Dedicated Preparation)

- *In the final two weeks, focus on review, practice questions, and endurance. Stay confident!*

Your dedicated prep time may be one week or two months. You should have a working plan as you go into this period. Finish your schoolwork strong, take a day off, and then get to work. Start by simulating a full-length USMLE Step 1 if you haven't yet done so. Consider doing one NBME CBSSA and the free questions from the NBME website. Alternatively, you could choose 7 blocks of randomized questions from a commercial question bank. Make sure you get feedback on your strengths and weaknesses and adjust your studying accordingly. Many students study from review sources or comprehensive programs for part of the day, then do question blocks. Also, keep in mind that reviewing a question block can take upward of two hours. Feedback from CBSSA exams and question banks will help you focus on your weaknesses.

One Week Prior

Make sure you have your CIN (found on your scheduling permit) as well as other items necessary for the day of the examination, including a current driver's license or another form of photo ID with your signature (make sure the name on your **ID exactly** matches that on your scheduling permit). Confirm the Prometric testing center location and test time. Work out how you will get to the testing center and what parking and traffic problems you might encounter. Drive separately from other students taking the test on the same day, and exchange cell phone numbers in case of emergencies. If possible, visit the testing site to get a better idea of the testing conditions you will face. Determine what you will do for lunch. Make sure you have everything you need to ensure that you will be comfortable and alert at the test site. It may be beneficial to adjust your schedule to start waking up at the same time that you will on your test day. And of course, make sure to maintain a healthy lifestyle and get enough sleep.

- *One week before the test:*
  - *Sleep according to the same schedule you'll use on test day*
  - *Review the CBT tutorial one last time*
  - *Call Prometric to confirm test date and time*

One Day Prior

Try your best to relax and rest the night before the test. Double-check your admissions and test-taking materials as well as the comfort measures discussed earlier so that you will not have to deal with such details on the morning of the exam. At this point it will be more effective to review short-term memory material that you're already familiar with than to try to learn new material. The Rapid Review section at the end of this book is high yield for last-minute studying. Remember that regardless of how hard you have studied, you cannot know everything. There will be things on the exam that you have never even seen before, so do not panic. Do not underestimate your abilities.

Many students report difficulty sleeping the night prior to the exam. This is often exacerbated by going to bed much earlier than usual. Do whatever it takes to ensure a good night's sleep (eg, massage, exercise, warm milk, no back-lit screens at night). Do not change your daily routine prior to the exam. Exam day is not the day for a caffeine-withdrawal headache.

Morning of the Exam

On the morning of the Step 1 exam, wake up at your regular time and eat a normal breakfast. If you think it will help you, have a close friend or family member check to make sure you get out of bed. Make sure you have your scheduling permit admission ticket, test-taking materials, and comfort measures as discussed earlier. Wear loose, comfortable clothing. Plan for a variable temperature in the testing center. Arrive at the test site 30 minutes before the time designated on the admission ticket; however, do not come too early, as doing so may intensify your anxiety. When you arrive at the test site, the proctor should give you a USMLE information sheet that will explain critical factors such as the proper use of break time. Seating may be assigned, but ask to be reseated if necessary; you need to be seated in an area that will allow you to remain comfortable and to concentrate. Get to know your testing station, especially if you have never been in a Prometric testing center before. Listen to your proctors regarding any changes in instructions or testing procedures that may apply to your test site.

- *No notes, books, calculators, pagers, cell phones, recording devices, or watches of any kind are allowed in the testing area, but they are allowed in lockers.*

- *Arrive at the testing center 30 minutes before your scheduled exam time. If you arrive more than half an hour late, you will not be allowed to take the test.*

Finally, remember that it is natural (and even beneficial) to be a little nervous. Focus on being mentally clear and alert. Avoid panic. When you are asked to begin the exam, take a deep breath, focus on the screen, and then begin. Keep an eye on the timer. Take advantage of breaks between blocks to stretch, maybe do some jumping jacks, and relax for a moment with deep breathing or stretching.

After the Test

After you have completed the exam, be sure to have fun and relax regardless of how you may feel. Taking the test is an achievement in itself. Remember, you are much more likely to have passed than not. Enjoy the free time you have before your clerkships. Expect to experience some "reentry" phenomena as you try to regain a real life. Once you have recovered sufficiently from the test (or from partying), we invite you to send us your feedback, corrections, and suggestions for entries, facts, mnemonics, strategies, resource ratings, and the like (see p. xvii, How to Contribute). Sharing your experience will benefit fellow medical students and IMGs.

▶ STUDY MATERIALS

Quality Considerations

Although an ever-increasing number of review books and software are now available on the market, the quality of such material is highly variable. Some common problems are as follows:

- Certain review books are too detailed to allow for review in a reasonable amount of time or cover subtopics that are not emphasized on the exam.
- Many sample question books were originally written years ago and have not been adequately updated to reflect recent trends.
- Some question banks test to a level of detail that you will not find on the exam.

▶ *If a given review book is not working for you, stop using it no matter how highly rated it may be or how much it costs.*

Review Books

In selecting review books, be sure to weigh different opinions against each other, read the reviews and ratings in Section IV of this guide, examine the books closely in the bookstore, and choose carefully. You are investing not only money but also your limited study time. Do not worry about finding the "perfect" book, as many subjects simply do not have one, and different students prefer different formats. Supplement your chosen books with personal notes from other sources, including what you learn from question banks.

There are two types of review books: those that are stand-alone titles and those that are part of a series. Books in a series generally have the same style, and you must decide if that style works for you. However, a given style is not optimal for every subject.

- *Charts and diagrams may be the best approach for physiology and biochemistry, whereas tables and outlines may be preferable for microbiology.*

You should also find out which books are up to date. Some recent editions reflect major improvements, whereas others contain only cursory changes. Take into consideration how a book reflects the format of the USMLE Step 1.

Apps

With the explosion of smartphones and tablets, apps are an increasingly popular way to review for the Step 1 exam. The majority of apps are compatible with both iOS and Android. Many popular Step 1 review resources (eg, UWorld, USMLE-Rx) have apps that are compatible with their software. Many popular web references (eg, UpToDate) also now offer app versions. All of these apps offer flexibility, allowing you to study while away from a computer (eg, while traveling).

Practice Tests

Taking practice tests provides valuable information about potential strengths and weaknesses in your fund of knowledge and test-taking skills. Some students use practice examinations simply as a means of breaking up the monotony of studying and adding variety to their study schedule, whereas other students rely almost solely on practice. You should also subscribe to one or more high-quality question banks. In addition, students report that many current practice-exam books have questions that are, on average, shorter and less clinically oriented than those on the current USMLE Step 1.

- *Most practice exams are shorter and less clinical than the real thing.*

Additionally, some students preparing for the Step 1 exam have started to incorporate case-based books intended primarily for clinical students on the wards or studying for the Step 2 CK exam. *First Aid Cases for the USMLE Step 1* aims to directly address this need.

After taking a practice test, spend time on each question and each answer choice whether you were right or wrong. There are important teaching points in each explanation. Knowing why a wrong answer choice is incorrect is just as important as knowing why the right answer is correct. Do not panic if your practice scores are low as many questions try to trick or distract you to highlight a certain point. Use the questions you missed or were unsure about to develop focused plans during your scheduled catch-up time.

- *Use practice tests to identify concepts and areas of weakness, not just facts that you missed.*

Textbooks and Course Syllabi

Limit your use of textbooks and course syllabi for Step 1 review. Many textbooks are too detailed for high-yield review and include material that is generally not tested on the USMLE Step 1 (eg, drug dosages, complex chemical structures). Syllabi, although familiar, are inconsistent across medical schools and frequently reflect the emphasis of individual faculty, which often does not correspond to that of the USMLE Step 1. Syllabi also tend to be less organized than top-rated books and generally contain fewer diagrams and study questions.

▶ TEST-TAKING STRATEGIES

▶ *Practice! Develop your test-taking skills and strategies well before the test date.*

Your test performance will be influenced by both your knowledge and your test-taking skills. You can strengthen your performance by considering each of these factors. Test-taking skills and strategies should be developed and perfected well in advance of the test date so that you can concentrate on the test itself. We suggest that you try the following strategies to see if they might work for you.

Pacing

You have seven hours to complete 280 questions. Note that each one-hour block contains up to 40 questions. This works out to approximately 90 seconds per question. We recommend following the "1 minute rule" to pace yourself. Spend no more than 1 minute on each question. If you are still unsure about the answer after this time, mark the question, make an educated guess, and move on. Following this rule, you should have approximately 20 minutes left after all questions are answered, which you can use to revisit all of your marked questions. Remember that some questions may be experimental and do not count for points (and reassure yourself that these experimental questions are the ones that are stumping you). In the past, pacing errors have been detrimental to the performance of even highly prepared examinees. The bottom line is to keep one eye on the clock at all times!

▶ *Time management is an important skill for exam success.*

Dealing with Each Question

There are several established techniques for efficiently approaching multiple choice questions; find what works for you. One technique begins with identifying each question as easy, workable, or impossible. Your goal should be to answer all easy questions, resolve all workable questions in a reasonable amount of time, and make quick and intelligent guesses on all impossible questions. Most students read the stem, think of the answer, and turn immediately to the choices. A second technique is to first skim the answer choices to get a context, then read the last sentence of the question (the lead-in), and then read through the passage quickly, extracting only information relevant to answering the question. This can be particularly helpful for questions with long clinical vignettes. Try a variety of techniques on practice exams and see what works best for you. If you get overwhelmed, remember that a 30-second time out to refocus may get you back on track.

Guessing

There is **no penalty** for wrong answers. Thus, **no test block should be left with unanswered questions.** A hunch is probably better than a random guess. If you have to guess, we suggest selecting an answer you recognize over one with which you are totally unfamiliar.

Changing Your Answer

The conventional wisdom is not to change answers that you have already marked unless there is a convincing and logical reason to do so—in other words, go with your "first hunch." Many question banks tell you how many questions you changed from right to wrong, wrong to wrong, and wrong to right. Use this feedback to judge how good a second-guesser you are. If you have extra time, reread the question stem and make sure you didn't misinterpret the question.

▸ *Go with your first hunch, unless you are certain that you are a good second-guesser.*

▸ CLINICAL VIGNETTE STRATEGIES

In recent years, the USMLE Step 1 has become increasingly clinically oriented. This change mirrors the trend in medical education toward introducing students to clinical problem solving during the basic science years. The increasing clinical emphasis on Step 1 may be challenging to those students who attend schools with a more traditional curriculum.

▸ *Be prepared to read fast and think on your feet!*

What Is a Clinical Vignette?

A clinical vignette is a short (usually paragraph-long) description of a patient, including demographics, presenting symptoms, signs, and other information concerning the patient. Sometimes this paragraph is followed by a brief listing of important physical findings and/or laboratory results. The task of assimilating all this information and answering the associated question in the span of one minute can be intimidating. So be prepared to read quickly and think on your feet. Remember that the question is often indirectly asking something you already know.

▸ *Practice questions that include case histories or descriptive vignettes are critical for Step 1 preparation.*

Strategy

Remember that Step 1 vignettes usually describe diseases or disorders in their most classic presentation. So look for cardinal signs (eg, malar rash for SLE or nuchal rigidity for meningitis) in the narrative history. Be aware that the question will contain classic signs and symptoms instead of buzzwords. Sometimes the data from labs and the physical exam will help you confirm or reject possible diagnoses, thereby helping you rule answer choices in or out. In some cases, they will be a dead giveaway for the diagnosis.

▸ *Step 1 vignettes usually describe diseases or disorders in their most classic presentation.*

Making a diagnosis from the history and data is often not the final answer. Not infrequently, the diagnosis is divulged at the end of the vignette, after you have just struggled through the narrative to come up with a diagnosis of your own. The question might then ask about a related aspect of the diagnosed disease. Consider skimming the answer choices and lead-in before diving into a long stem. However, be careful with skimming the answer choices; going too fast may warp your perception of what the vignette is asking.

▶ IF YOU THINK YOU FAILED

After the test, many examinees feel that they have failed, and most are at the very least unsure of their pass/fail status. There are several sensible steps you can take to plan for the future in the event that you do not achieve a passing score. First, save and organize all your study materials, including review books, practice tests, and notes. Familiarize yourself with the reapplication procedures for Step 1, including application deadlines and upcoming test dates.

▶ *If you pass Step 1 (score of 192 or above), you are not allowed to retake the exam.*

Make sure you know both your school's and the NBME's policies regarding retakes. The NBME allows a maximum of six attempts to pass each Step examination.[11] You may take Step 1 no more than three times within a 12-month period. Your fourth and subsequent attempts must be at least 12 months after your first attempt at that exam and at least six months after your most recent attempt at that exam.

The performance profiles on the back of the USMLE Step 1 score report provide valuable feedback concerning your relative strengths and weaknesses. Study these profiles closely. Set up a study timeline to strengthen gaps in your knowledge as well as to maintain and improve what you already know. Do not neglect high-yield subjects. It is normal to feel somewhat anxious about retaking the test, but if anxiety becomes a problem, seek appropriate counseling.

▶ TESTING AGENCIES

- **National Board of Medical Examiners (NBME) / USMLE Secretariat**
  Department of Licensing Examination Services
  3750 Market Street
  Philadelphia, PA 19104-3102
  (215) 590-9500 (operator) or
  (215) 590-9700 (automated information line)
  Fax: (215) 590-9457
  Email: webmail@nbme.org
  www.nbme.org

- **Educational Commission for Foreign Medical Graduates (ECFMG)**
  3624 Market Street
  Philadelphia, PA 19104-2685
  (215) 386-5900
  Fax: (215) 386-9196
  Email: info@ecfmg.org
  www.ecfmg.org

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NOTES

SECTION I SUPPLEMENT

Special Situations

Please visit **www.firstaidteam.com/bonus/** to view this section.

- First Aid for the International Medical Graduate 2
- First Aid for the Osteopathic Medical Student 13
- First Aid for the Podiatric Medical Student 17
- First Aid for the Student Requiring Test Accommodations 19

▶ NOTES

SECTION II

High-Yield General Principles

"There comes a time when for every addition of knowledge you forget something that you knew before. It is of the highest importance, therefore, not to have useless facts elbowing out the useful ones."

—Sir Arthur Conan Doyle, A *Study in Scarlet*

"Never regard study as a duty, but as the enviable opportunity to learn."

—Albert Einstein

"Live as if you were to die tomorrow. Learn as if you were to live forever."

—Gandhi

- How to Use the Database 28
- Biochemistry 31
- Immunology 91
- Microbiology 119
- Pathology 203
- Pharmacology 223
- Public Health Sciences 245

▶ HOW TO USE THE DATABASE

The 2017 edition of *First Aid for the USMLE Step 1* contains a revised and expanded database of basic science material that students, student authors, and faculty authors have identified as high yield for board review. The information is presented in a partially organ-based format. Hence, Section II is devoted to the foundational principles of biochemistry, microbiology, immunology, basic pathology, basic pharmacology, and public health sciences. Section III focuses on organ systems, with subsections covering the embryology, anatomy and histology, physiology, clinical pathology, and clinical pharmacology relevant to each. Each subsection is then divided into smaller topic areas containing related facts. Individual facts are generally presented in a three-column format, with the **Title** of the fact in the first column, the **Description** of the fact in the second column, and the **Mnemonic** or **Special Note** in the third column. Some facts do not have a mnemonic and are presented in a two-column format. Others are presented in list or tabular form in order to emphasize key associations.

The database structure used in Sections II and III is useful for reviewing material already learned. These sections are **not** ideal for learning complex or highly conceptual material for the first time.

The database of high-yield facts is not comprehensive. Use it to complement your core study material and not as your primary study source. The facts and notes have been condensed and edited to emphasize the essential material, and as a result, each entry is "incomplete" and arguably "over-simplified." Often, the more you research a topic, the more complex it becomes, with certain topics resisting simplification. Work with the material, add your own notes and mnemonics, and recognize that not all memory techniques work for all students.

We update the database of high-yield facts annually to keep current with new trends in boards emphasis, including clinical relevance. However, we must note that inevitably many other high-yield topics are not yet included in our database.

We actively encourage medical students and faculty to submit high-yield topics, well-written entries, diagrams, clinical images, and useful mnemonics so that we may enhance the database for future students. We also solicit recommendations of alternate tools for study that may be useful in preparing for the examination, such as charts, flash cards, apps, and online resources (see How to Contribute, p. xvii).

Image Acknowledgments

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Disclaimer

The entries in this section reflect student opinions of what is high yield. Because of the diverse sources of material, no attempt has been made to trace or reference the origins of entries individually. We have regarded mnemonics as essentially in the public domain. Errata will gladly be corrected if brought to the attention of the authors, either through our online errata submission form at www.firstaidteam.com or directly by email to firstaidteam@yahoo.com.

NOTES

HIGH-YIELD PRINCIPLES IN

Biochemistry

"Biochemistry is the study of carbon compounds that crawl."

—Mike Adams

"We think we have found the basic mechanism by which life comes from life."

—Francis H. C. Crick

"The biochemistry and biophysics are the notes required for life; they conspire, collectively, to generate the real unit of life, the organism."

—Ursula Goodenough

This high-yield material includes molecular biology, genetics, cell biology, and principles of metabolism (especially vitamins, cofactors, minerals, and single-enzyme-deficiency diseases). When studying metabolic pathways, emphasize important regulatory steps and enzyme deficiencies that result in disease, as well as reactions targeted by pharmacologic interventions. For example, understanding the defect in Lesch-Nyhan syndrome and its clinical consequences is higher yield than memorizing every intermediate in the purine salvage pathway. Do not spend time on hard-core organic chemistry, mechanisms, or physical chemistry. Detailed chemical structures are infrequently tested; however, many structures have been included here to help students learn reactions and the important enzymes involved. Familiarity with the biochemical techniques that have medical relevance—such as ELISA, immunoelectrophoresis, Southern blotting, and PCR—is useful. Review the related biochemistry when studying pharmacology or genetic diseases as a way to reinforce and integrate the material.

▸ Molecular 32

▸ Cellular 42

▸ Laboratory Techniques 48

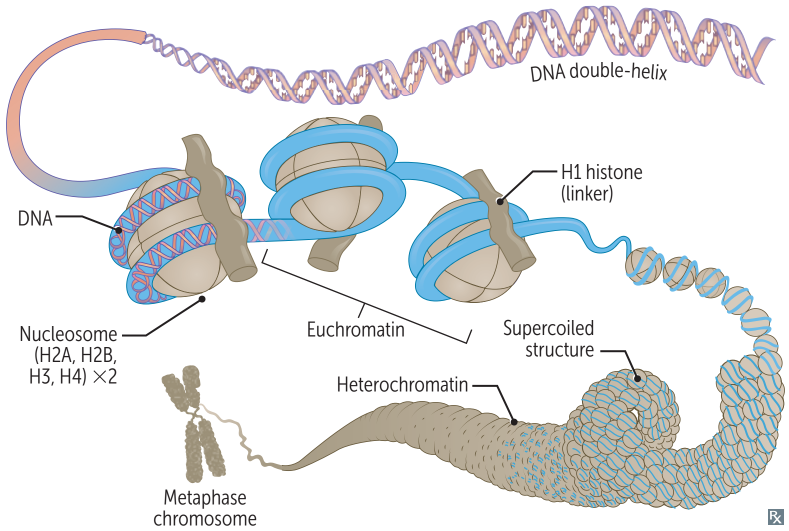
▸ Genetics 52

▸ Nutrition 61

▸ Metabolism 68

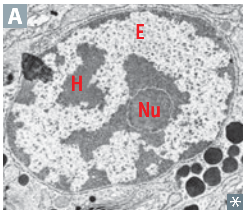
▸ BIOCHEMISTRY—MOLECULAR

Chromatin structure



DNA exists in the condensed, chromatin form in order to fit into the nucleus. Negatively charged DNA loops twice around positively charged histone octamer to form nucleosome "**beads on a string**." Histones are rich in the amino acids lysine and arginine. H1 binds to the nucleosome and to "linker DNA," thereby stabilizing the chromatin fiber.

In mitosis, DNA condenses to form chromosomes. DNA and histone synthesis occur during S phase.

Heterochromatin 	Condensed, appears darker on EM (labeled H in A). Transcriptionally inactive, sterically inaccessible. ↑ methylation, ↓ acetylation.	**H**etero**C**hromatin = **H**ighly **C**ondensed. Barr bodies (inactive X chromosomes) are heterochromatin.
Euchromatin	Less condensed, appears lighter on EM (labeled E in A). Transcriptionally active, sterically accessible.	*Eu* = true, "truly transcribed." **E**uchromatin is **E**xpressed.
DNA methylation	Template strand cytosine and adenine are methylated in DNA replication, which allows mismatch repair enzymes to distinguish between old and new strands in prokaryotes.	
	DNA methylation at CpG islands represses transcription.	CpG **M**ethylation **M**akes DNA **M**ute.
Histone methylation	Usually reversibly represses DNA transcription, but can activate it in some cases depending on methylation location.	Histone **M**ethylation **M**ostly **M**akes DNA **M**ute.
Histone acetylation	Relaxes DNA coiling, allowing for transcription.	Histone **A**cetylation makes DNA **A**ctive.

Nucleotides

Nucleo**S**ide = base + (deoxy)ribose (**S**ugar).

Nucleo**T**ide = base + (deoxy)ribose + phospha**T**e; linked by 3′-5′ phosphodiester bond.

5′ end of incoming nucleotide bears the triphosphate (energy source for the bond). Triphosphate bond is target of 3′ hydroxyl attack.

PURines (**A**,**G**)—2 rings.

PYrimidines (**C**,**U**,**T**)—1 ring.

PURe **A**s **G**old.

CUT the **PY** (pie).

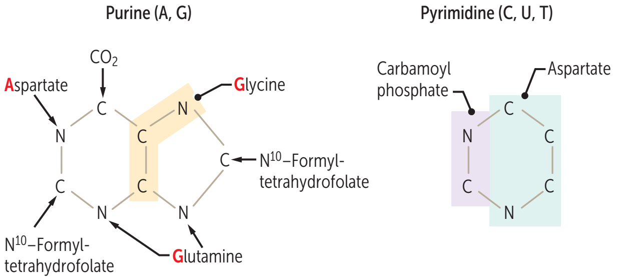
Thymine has a met**hyl**.

Deamination of cytosine makes uracil.

Deamination of adenine makes guanine.

Uracil found in RNA; thymine in DNA. Methylation of uracil makes thymine.

G-C bond (3 H bonds) stronger than A-T bond (2 H bonds). ↑ G-C content → ↑ melting temperature of DNA. “**C**-**G** bonds are like **C**razy **G**lue.”


Purine (A, G)
CO2
Aspartate
Glycine
N
C
N10–Formyl-tetrahydrofolate
Glutamine
Pyrimidine (C, U, T)
Carbamoyl phosphate
Aspartate

GAG—Amino acids necessary for purine synthesis:

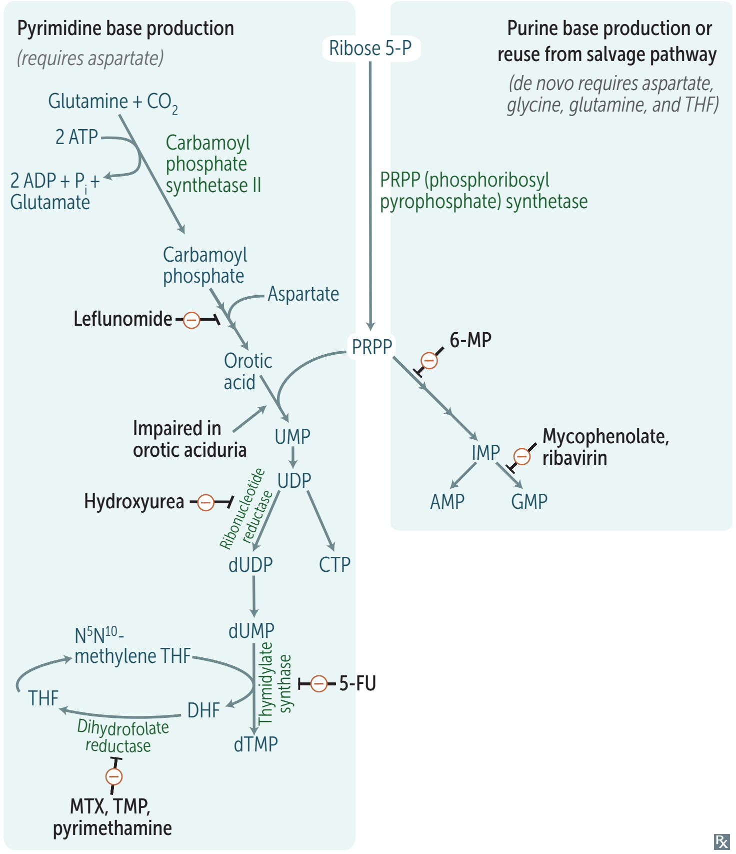
Glycine

Aspartate

Glutamine

De novo pyrimidine and purine synthesis

Various immunosuppressive, antineoplastic, and antibiotic drugs function by interfering with nucleotide synthesis:


Pyrimidine base production
(requires aspartate)
Glutamine + CO2
2 ATP
2 ADP + Pi + Glutamate
Carbamoyl phosphate synthetase II
Carbamoyl phosphate
Aspartate
Leflunomide
Orotic acid
Impaired in orotic aciduria
UMP
UDP
Hydroxyurea
Ribonucleotide reductase
dUDP
CTP
dUMP
N5N10-methylene THF
THF
DHF
Dihydrofolate reductase
MTX, TMP, pyrimethamine
Thymidylate synthase
5-FU
dTMP
Ribose 5-P
PRPP (phosphoribosyl pyrophosphate) synthetase
PRPP
Purine base production or reuse from salvage pathway
(de novo requires aspartate, glycine, glutamine, and THF)
6-MP
IMP
Mycophenolate, ribavirin
AMP
GMP

Disrupt pyrimidine synthesis:

- Leflunomide: inhibits dihydroorotate dehydrogenase
- Methotrexate (MTX), trimethoprim (TMP), and pyrimethamine: inhibit dihydrofolate reductase (↓ deoxythymidine monophosphate [dTMP]) in humans, bacteria, and protozoa, respectively
- 5-fluorouracil (5-FU): forms 5-F-dUMP, which inhibits thymidylate synthase (↓ dTMP)

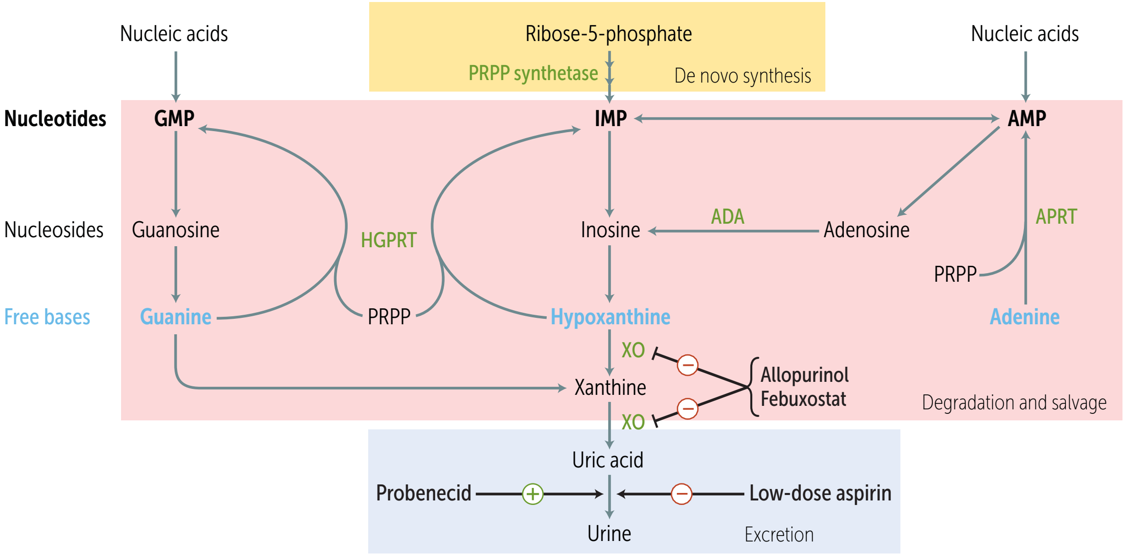
Disrupt purine synthesis:

- 6-mercaptopurine (6-MP) and its prodrug azathioprine: inhibit de novo purine synthesis
- Mycophenolate and ribavirin: inhibit inosine monophosphate dehydrogenase

Disrupts purine and pyrimidine synthesis:

- Hydroxyurea: inhibits ribonucleotide reductase

Purine salvage deficiencies


Nucleic acids
Ribose-5-phosphate
PRPP synthetase
De novo synthesis
Nucleic acids
Nucleotides
GMP
IMP
AMP
Nucleosides
Guanosine
HGPRT
Inosine
ADA
Adenosine
APRT
PRPP
Free bases
Guanine
PRPP
Hypoxanthine
Adenine
XO
Xanthine
Allopurinol
Febuxostat
XO
Degradation and salvage
Uric acid
Probenecid
Low-dose aspirin
Urine
Excretion

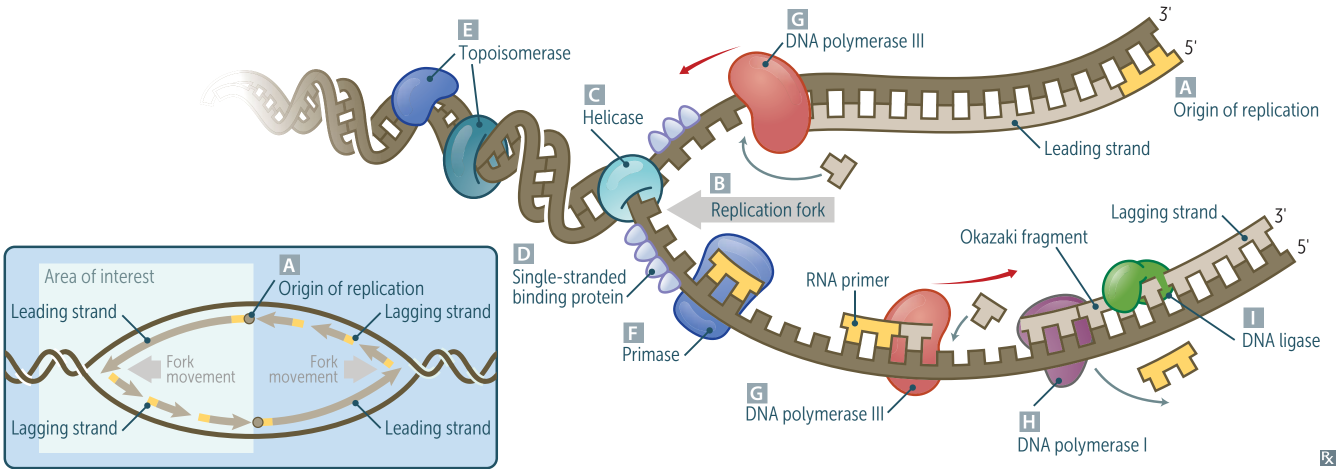
ADA, adenosine deaminase; APRT, adenine phosphoribosyltransferase;
HGPRT, hypoxanthine guanine phosphoribosyltransferase; XO, xanthine oxidase.

Adenosine deaminase deficiency	ADA is required for degradation of adenosine and deoxyadenosine. In ADA deficiency, ↑ dATP → toxicity in lymphocytes.	One of the major causes of autosomal recessive SCID.
Lesch-Nyhan syndrome	Defective purine salvage due to absent **HGPRT**, which converts hypoxanthine to IMP and guanine to GMP. Results in excess uric acid production and de novo purine synthesis. X-linked recessive. Findings: intellectual disability, self-mutilation, aggression, hyperuricemia (orange “sand” [sodium urate crystals] in diaper), gout, dystonia. Treatment: allopurinol or febuxostat (2nd line).	**HGPRT**: **H**yperuricemia **G**out **P**issed off (aggression, self-mutilation) **R**etardation (intellectual disability) Dys**T**onia

Genetic code features

Unambiguous	Each codon specifies only 1 amino acid.	
Degenerate/ redundant	Most amino acids are coded by multiple codons. **Wobble**—codons that differ in 3rd, “wobble” position may code for the same tRNA/amino acid. Specific base pairing is usually only required in the first 2 nucleotide positions of mRNA codon.	Exceptions: methionine and tryptophan encoded by only 1 codon (AUG and UGG, respectively).
Commaless, nonoverlapping	Read from a fixed starting point as a continuous sequence of bases.	Exceptions: some viruses.
Universal	Genetic code is conserved throughout evolution.	Exception in humans: mitochondria.

DNA replication	Eukaryotic DNA replication is more complex than the prokaryotic process but uses many enzymes analogous to those listed below. In both prokaryotes and eukaryotes, DNA replication is semiconservative, involves both continuous and discontinuous (Okazaki fragment) synthesis, and occurs in the 5′ → 3′ direction.	
Origin of replication A	Particular consensus sequence of base pairs in genome where DNA replication begins. May be single (prokaryotes) or multiple (eukaryotes).	AT-rich sequences (such as TATA box regions) are found in promoters and origins of replication.
Replication fork B	Y-shaped region along DNA template where leading and lagging strands are synthesized.	
Helicase C	Unwinds DNA template at replication fork.	
Single-stranded binding proteins D	Prevent strands from reannealing.	
DNA topoisomerases E	Create a single- or double-stranded break in the helix to add or remove supercoils.	Irinotecan/topotecan inhibit eukaryotic topoisomerase I. Etoposide/teniposide inhibit eukaryotic topoisomerase II. Fluoroquinolones inhibit prokaryotic topoisomerase II (DNA gyrase) and topoisomerase IV.
Primase F	Makes an RNA primer on which DNA polymerase III can initiate replication.	
DNA polymerase III G	Prokaryotes only. Elongates leading strand by adding deoxynucleotides to the 3′ end. Elongates lagging strand until it reaches primer of preceding fragment. 3′ → 5′ exonuclease activity “proofreads” each added nucleotide.	DNA polymerase III has 5′ → 3′ synthesis and proofreads with 3′ → 5′ exonuclease. Drugs blocking DNA replication often have a modified 3′ OH, thereby preventing addition of the next nucleotide (“chain termination”).
DNA polymerase I H	Prokaryotic only. Degrades RNA primer; replaces it with DNA.	Same functions as DNA polymerase III, also excises RNA primer with 5′ → 3′ exonuclease.
DNA ligase I	Catalyzes the formation of a phosphodiester bond within a strand of double-stranded DNA.	Joins Okazaki fragments.
Telomerase	Eukaryotes only. An RNA-dependent DNA polymerase that adds DNA to 3′ ends of chromosomes to avoid loss of genetic material with every duplication.	Often dysregulated in cancer cells, allowing unlimited replication.

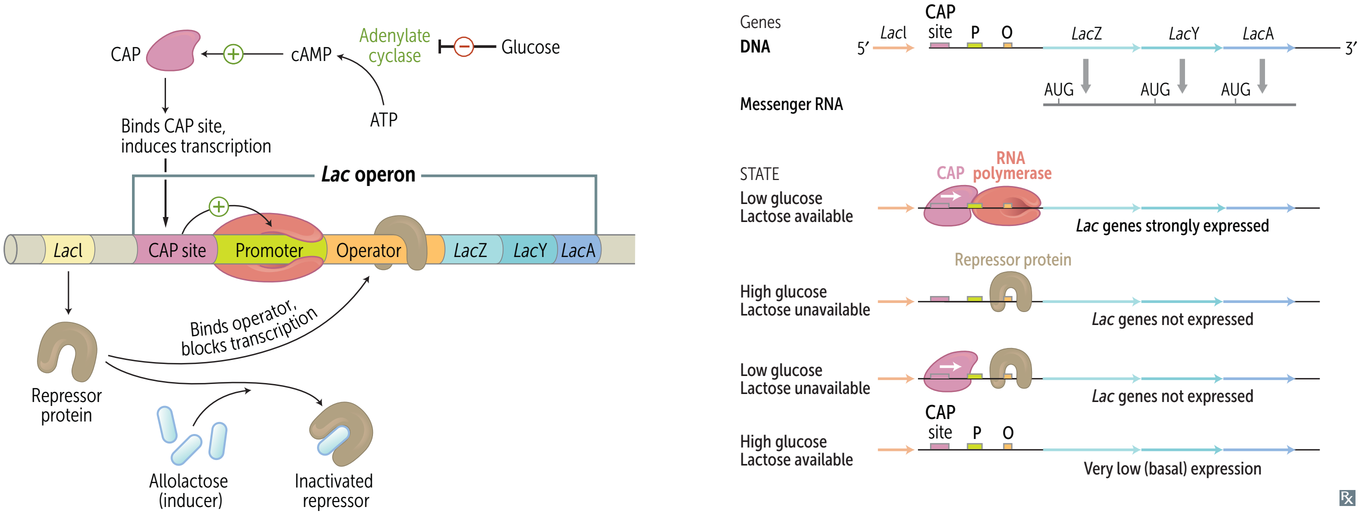

E Topoisomerase
G DNA polymerase III
3'
5'
A Origin of replication
C Helicase
Leading strand
B Replication fork
Lagging strand
3'
5'
Okazaki fragment
D Single-stranded binding protein
RNA primer
I DNA ligase
F Primase
G DNA polymerase III
H DNA polymerase I
Area of interest
A Origin of replication
Leading strand
Lagging strand
Fork movement
Fork movement
Lagging strand
Leading strand
℞

Mutations in DNA	Severity of damage: silent << missense < nonsense < frameshift. For point (silent, missense, and nonsense) mutations: - Transition—purine to purine (eg, A to G) or pyrimidine to pyrimidine (eg, C to T). - Transversion—purine to pyrimidine (eg, A to T) or pyrimidine to purine (eg, C to G).	
Silent	Nucleotide substitution but codes for same (synonymous) amino acid; often base change in 3rd position of codon (tRNA wobble).	
Missense	Nucleotide substitution resulting in changed amino acid (called conservative if new amino acid is similar in chemical structure).	Sickle cell disease (substitution of glutamic acid with valine).
Nonsense	Nucleotide substitution resulting in early **stop** codon (UAG, UAA, UGA). Usually results in nonfunctional protein.	**Stop** the **nonsense**!
Frameshift	Deletion or insertion of a number of nucleotides not divisible by 3, resulting in misreading of all nucleotides downstream. Protein may be shorter or longer, and its function may be disrupted or altered.	Duchenne muscular dystrophy, Tay-Sachs disease.
Splice site	Mutation at a splice site → retained intron in the mRNA → protein with impaired or altered function.	Rare cause of cancers, dementia, epilepsy, some types of β-thalassemia.

***Lac* operon**

Classic example of a genetic response to an environmental change. Glucose is the preferred metabolic substrate in *E coli*, but when glucose is absent and lactose is available, the *lac* operon is activated to switch to lactose metabolism. Mechanism of shift:

- Low glucose → ↑ adenylate cyclase activity → ↑ generation of cAMP from ATP → activation of catabolite activator protein (CAP) → ↑ transcription.
- High lactose → unbinds repressor protein from repressor/operator site → ↑ transcription.


CAP
cAMP
Adenylate cyclase
Glucose
ATP
Binds CAP site, induces transcription
Lac operon
LacI
CAP site
Promoter
Operator
LacZ
LacY
LacA
Binds operator, blocks transcription
Repressor protein
Allolactose (inducer)
Inactivated repressor
Genes
DNA
5′
LacI
CAP site
P
O
LacZ
LacY
LacA
3′
AUG
AUG
AUG
Messenger RNA
STATE
Low glucose Lactose available
CAP
RNA polymerase
Lac genes strongly expressed
Repressor protein
High glucose Lactose unavailable
Lac genes not expressed
Low glucose Lactose unavailable
Lac genes not expressed
CAP site
P
O
High glucose Lactose available
Very low (basal) expression

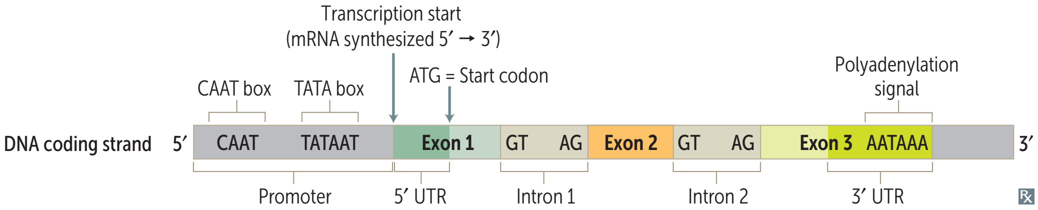
DNA repair

Single strand		
Nucleotide excision repair	Specific endonucleases release the oligonucleotides containing damaged bases; DNA polymerase and ligase fill and reseal the gap, respectively. Repairs bulky helix-distorting lesions. Occurs in G_1 phase of cell cycle.	Defective in xeroderma pigmentosum, which prevents repair of pyrimidine dimers that are formed as a result of ultraviolet light exposure.
Base excision repair	Base-specific **G**lycosylase removes altered base and creates AP site (apurinic/apyrimidinic). One or more nucleotides are removed by AP-**E**ndonuclease, which cleaves the 5′ end. **L**yase cleaves the 3′ end. DNA **P**olymerase-β fills the gap and DNA **L**igase seals it. Occurs throughout cell cycle.	Important in repair of spontaneous/toxic deamination. "**GEL PL**ease"
Mismatch repair	Newly synthesized strand is recognized, mismatched nucleotides are removed, and the gap is filled and resealed. Occurs predominantly in G_2 phase of cell cycle.	Defective in Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]).
Double strand		
Nonhomologous end joining	Brings together 2 ends of DNA fragments to repair double-stranded breaks. No requirement for homology. Some DNA may be lost.	Defective in ataxia telangiectasia, breast/ovarian cancers with *BRCA1* mutation, and Fanconi anemia.

Start and stop codons

mRNA start codons	AUG (or rarely GUG).	**AUG** in**AUG**urates protein synthesis.
Eukaryotes	Codes for methionine, which may be removed before translation is completed.	
Prokaryotes	Codes for N-formylmethionine (fMet).	fMet stimulates neutrophil chemotaxis.
mRNA stop codons	UGA, UAA, UAG.	**UGA** = **U G**o **A**way. **UAA** = **U A**re **A**way. **UAG** = **U A**re **G**one.

Functional organization of a eukaryotic gene


Transcription start
(mRNA synthesized 5′ → 3′)
ATG = Start codon
CAAT box
TATA box
Polyadenylation signal
DNA coding strand
5′
CAAT
TATAAT
Exon 1
GT
AG
Exon 2
GT
AG
Exon 3
AATAAA
3′
Promoter
5′ UTR
Intron 1
Intron 2
3′ UTR

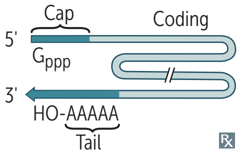
Regulation of gene expression

Promoter	Site where RNA polymerase II and multiple other transcription factors bind to DNA upstream from gene locus (AT-rich upstream sequence with TATA and CAAT boxes).	Promoter mutation commonly results in dramatic ↓ in level of gene transcription.
Enhancer	Stretch of DNA that alters gene expression by binding transcription factors (eg, activator proteins).	Enhancers and silencers may be located close to, far from, or even within (in an intron) the gene whose expression it regulates.
Silencer	Site where negative regulators (repressors) bind.	

RNA polymerases

Eukaryotes	RNA polymerase I makes **r**RNA (most numerous RNA, **r**ampant). RNA polymerase II makes **m**RNA (largest RNA, **m**assive). mRNA is read 5′ to 3′. RNA polymerase III makes 5S rRNA, **t**RNA (smallest RNA, **t**iny). No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site.	I, II, and III are numbered in the same order that their products are used in protein synthesis: rRNA, mRNA, then tRNA. α-amanitin, found in *Amanita phalloides* (death cap mushrooms), inhibits RNA polymerase II. Causes severe hepatotoxicity if ingested. Actinomycin D inhibits RNA polymerase in both prokaryotes and eukaryotes.
Prokaryotes	1 RNA polymerase (multisubunit complex) makes all 3 kinds of RNA.	Rifampin inhibits DNA-dependent RNA polymerase in prokaryotes.

RNA processing (eukaryotes)


Cap
Coding
5′
Gppp
3′
HO-AAAAA
Tail

Initial transcript is called heterogeneous nuclear RNA (hnRNA). hnRNA is then modified and becomes mRNA.

The following processes occur in the nucleus:

- Capping of 5′ end (addition of 7-methylguanosine cap)
- Polyadenylation of 3′ end (≈ 200 A's)
- Splicing out of introns

Capped, tailed, and spliced transcript is called mRNA.

mRNA is transported out of the nucleus into the cytosol, where it is translated.

mRNA quality control occurs at cytoplasmic processing bodies (P-bodies), which contain exonucleases, decapping enzymes, and microRNAs; mRNAs may be stored in P-bodies for future translation.

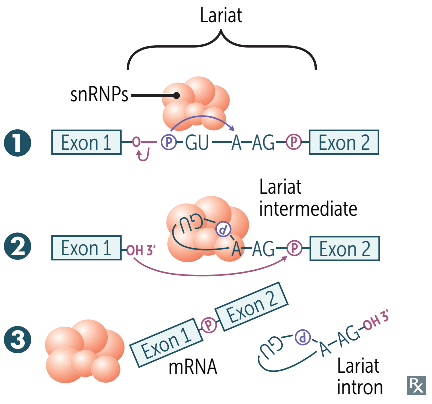
Poly-A polymerase does not require a template.

AAUAAA = polyadenylation signal.

Splicing of pre-mRNA

❶ Primary transcript combines with small nuclear ribonucleoproteins (snRNPs) and other proteins to form spliceosome.
❷ Lariat-shaped (looped) intermediate is generated.
❸ Lariat is released to precisely remove intron and join 2 exons.

Antibodies to spliceosomal snRNPs (anti-Smith antibodies) are highly specific for SLE. Anti-U1 RNP antibodies are highly associated with mixed connective tissue disease (MCTD).


Lariat
snRNPs
❶
Exon 1
P
GU
A
AG
P
Exon 2
Lariat intermediate
❷
Exon 1
OH 3′
GU
A
AG
P
Exon 2
❸
Exon 1
P
Exon 2
mRNA
GU
A
AG
OH 3′
Lariat intron

Introns vs exons

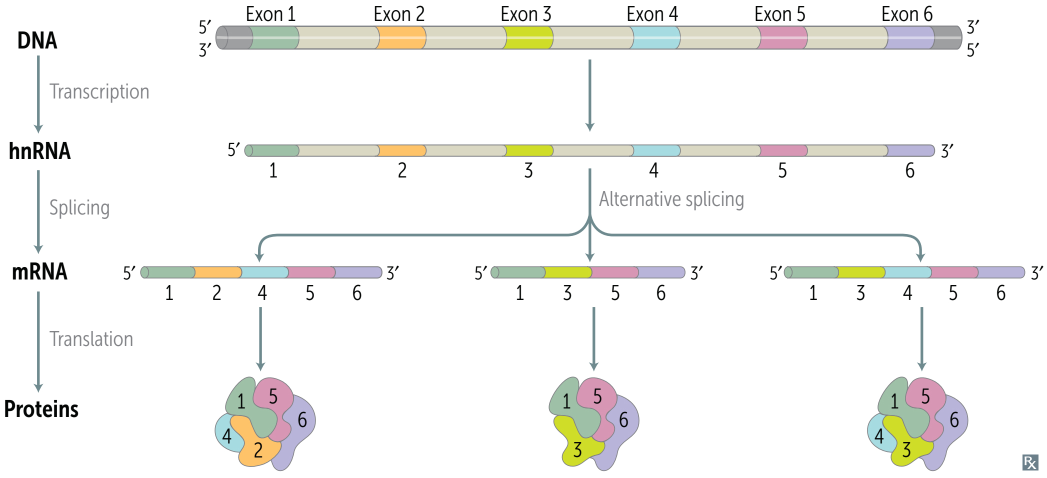
Exons contain the actual genetic information coding for protein.

Introns are intervening noncoding segments of DNA.

Different exons are frequently combined by alternative splicing to produce a larger number of unique proteins.

Introns are **in**tervening sequences and stay **in** the nucleus, whereas **ex**ons **ex**it and are **ex**pressed.

Abnormal splicing variants are implicated in oncogenesis and many genetic disorders (eg, β-thalassemia).


DNA
Transcription
hnRNA
Splicing
mRNA
Translation
Proteins
Exon 1
Exon 2
Exon 3
Exon 4
Exon 5
Exon 6
5′
3′
3′
5′
5′
1
2
3
4
5
6
3′
Alternative splicing
5′
1
2
4
5
6
3′
5′
1
3
5
6
3′
5′
1
3
4
5
6
3′
1
5
6
4
2
1
5
6
3
1
5
6
4
3

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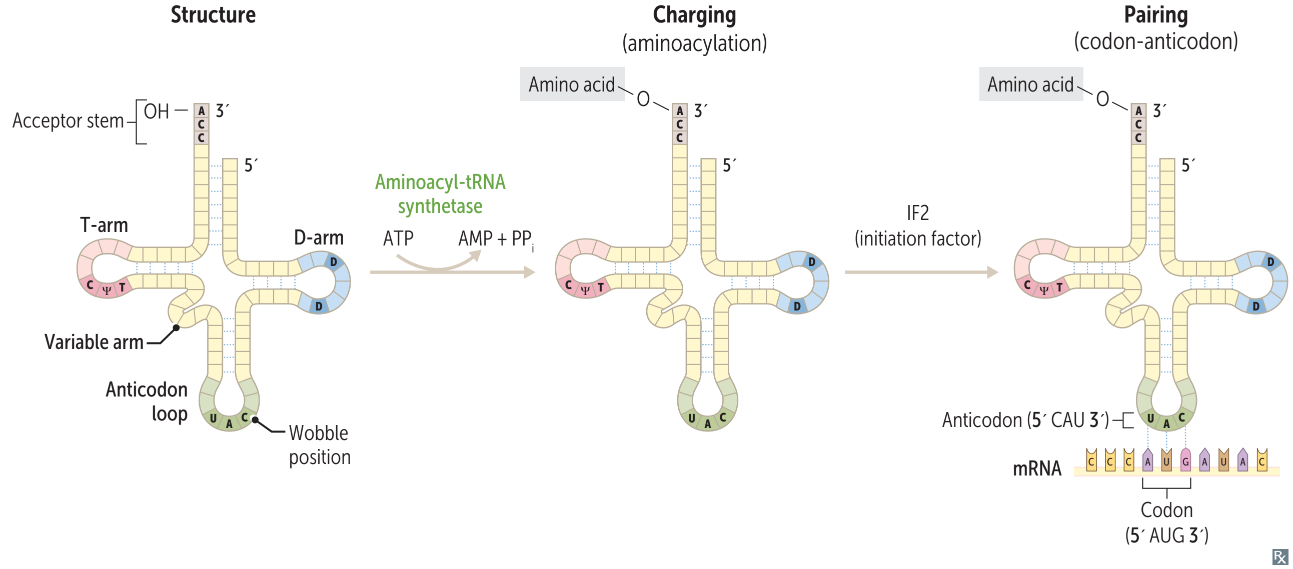
microRNAs

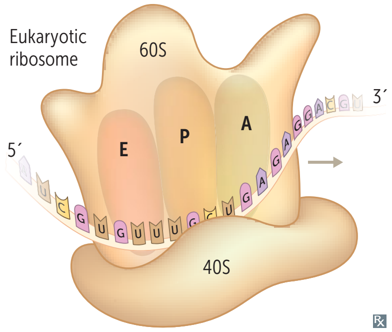
MicroRNAs (miRNA) are small, conserved, noncoding RNA molecules that posttranscriptionally regulate gene expression by targeting the 3′ untranslated region of specific mRNAs for degradation or translational repression. Abnormal expression of miRNAs contributes to certain malignancies (eg, by silencing an mRNA from a tumor suppressor gene).

tRNA

Structure	75–90 nucleotides, 2° structure, cloverleaf form, anticodon end is opposite 3′ aminoacyl end. All tRNAs, both eukaryotic and prokaryotic, have CCA at 3′ end along with a high percentage of chemically modified bases. The amino acid is covalently bound to the 3′ end of the tRNA. **CCA** **C**an **C**arry **A**mino acids. T-arm: contains the TΨC (ribothymidine, pseudouridine, cytidine) sequence necessary for tRNA-ribosome binding. **T**-arm **T**ethers tRNA molecule to ribosome. D-arm: contains dihydrouridine residues necessary for tRNA recognition by the correct aminoacyl-tRNA synthetase. **D**-arm **D**etects the tRNA by aminoacyl-tRNA synthetase. Acceptor stem: the 5′-CCA-3′ is the amino acid acceptor site.
Charging	Aminoacyl-tRNA synthetase (1 per amino acid; "matchmaker"; uses ATP) scrutinizes amino acid before and after it binds to tRNA. If incorrect, bond is hydrolyzed. The amino acid-tRNA bond has energy for formation of peptide bond. A mischarged tRNA reads usual codon but inserts wrong amino acid. Aminoacyl-tRNA synthetase and binding of charged tRNA to the codon are responsible for accuracy of amino acid selection.


Structure
Charging
(aminoacylation)
Pairing
(codon-anticodon)
Acceptor stem
OH
A
C
C
3′
5′
T-arm
C
Ψ
T
D-arm
D
D
Variable arm
Anticodon
loop
U
A
C
Wobble
position
Aminoacyl-tRNA
synthetase
ATP
AMP + PP$_i$
Amino acid
O
IF2
(initiation factor)
Anticodon (5′ CAU 3′)
mRNA
C C C A U G A U A C
Codon
(5′ AUG 3′)

Protein synthesis

Initiation	Initiated by GTP hydrolysis; initiation factors (eukaryotic IFs) help assemble the 40S ribosomal subunit with the initiator tRNA and are released when the mRNA and the ribosomal 60S subunit assemble with the complex.	**E**ukaryotes: 40S + 60S → 80S (**E**ven). Pr**O**karyotes: 30S + 50S → 70S (**O**dd). Synthesis occurs from N-terminus to C-terminus.
Elongation	1. Aminoacyl-tRNA binds to A site (except for initiator methionine) 2. rRNA (“ribozyme”) catalyzes peptide bond formation, transfers growing polypeptide to amino acid in A site 3. Ribosome advances 3 nucleotides toward 3′ end of mRNA, moving peptidyl tRNA to P site (translocation)	**A**TP—tRNA **A**ctivation (charging). **G**TP—tRNA **G**ripping and **G**oing places (translocation). Think of “going **APE**”: **A** site = incoming **A**minoacyl-tRNA. **P** site = accommodates growing **P**eptide. **E** site = holds **E**mpty tRNA as it **E**xits.
Termination	Stop codon is recognized by release factor, and completed polypeptide is released from ribosome.	 Eukaryotic ribosome 60S 40S E P A 5′ 3′

Posttranslational modifications

Trimming	Removal of N- or C-terminal propeptides from zymogen to generate mature protein (eg, trypsinogen to trypsin).
Covalent alterations	Phosphorylation, glycosylation, hydroxylation, methylation, acetylation, and ubiquitination.

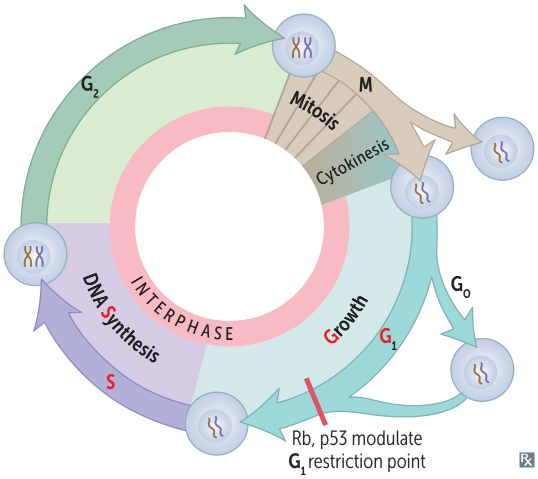
Chaperone protein	Intracellular protein involved in facilitating and/or maintaining protein folding. For example, in yeast, heat shock proteins (eg, HSP60) are expressed at high temperatures to prevent protein denaturing/misfolding.

▸ BIOCHEMISTRY—CELLULAR

Cell cycle phases	Checkpoints control transitions between phases of cell cycle. This process is regulated by cyclins, cyclin-dependent kinases (CDKs), and tumor suppressors. M phase (shortest phase of cell cycle) includes mitosis (prophase, prometaphase, metaphase, anaphase, telophase) and cytokinesis (cytoplasm splits in two). G_1 and G_0 are of variable duration.

REGULATION OF CELL CYCLE

Cyclin-dependent kinases	Constitutive and inactive.
Cyclins	Regulatory proteins that control cell cycle events; phase specific; activate CDKs.
Cyclin-CDK complexes	Phosphorylate other proteins to coordinate cell cycle progression; must be activated and inactivated at appropriate times for cell cycle to progress.
Tumor suppressors	p53 induces p21, which inhibits CDKs → hypophosphorylation (activation) of Rb → inhibition of G_1-S progression. Mutations in tumor suppressor genes can result in unrestrained cell division (eg, Li-Fraumeni syndrome).



CELL TYPES

Permanent	Remain in G_0, regenerate from stem cells.	Neurons, skeletal and cardiac muscle, RBCs.
Stable (quiescent)	Enter G_1 from G_0 when stimulated.	Hepatocytes, lymphocytes.
Labile	Never go to G_0, divide rapidly with a short G_1. Most affected by chemotherapy.	Bone marrow, gut epithelium, skin, hair follicles, germ cells.

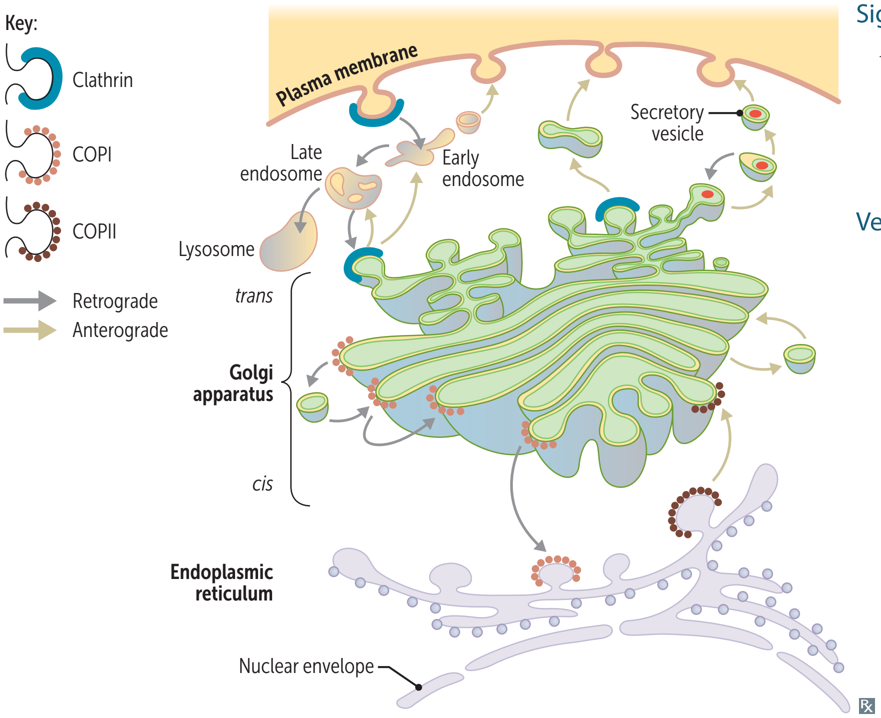
Rough endoplasmic reticulum	Site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to many proteins. Nissl bodies (RER in neurons)—synthesize peptide neurotransmitters for secretion. Free ribosomes—unattached to any membrane; site of synthesis of cytosolic and organellar proteins.	Mucus-secreting goblet cells of the small intestine and antibody-secreting plasma cells are rich in RER.
Smooth endoplasmic reticulum	Site of steroid synthesis and detoxification of drugs and poisons. Lacks surface ribosomes.	Liver hepatocytes and steroid hormone–producing cells of the adrenal cortex and gonads are rich in SER.

Cell trafficking

Golgi is the distribution center for proteins and lipids from the ER to the vesicles and plasma membrane. Modifies N-oligosaccharides on asparagine. Adds O-oligosaccharides on serine and threonine. Adds mannose-6-phosphate to proteins for trafficking to lysosomes.

Endosomes are sorting centers for material from outside the cell or from the Golgi, sending it to lysosomes for destruction or back to the membrane/Golgi for further use.

I-cell disease (inclusion cell disease/mucolipidosis type II)—inherited lysosomal storage disorder; defect in *N*-acetylglucosaminyl-1-phosphotransferase → failure of the Golgi to phosphorylate mannose residues (ie, ↓ mannose-6-phosphate) on glycoproteins → proteins are secreted extracellularly rather than delivered to lysosomes. Results in coarse facial features, clouded corneas, restricted joint movement, and high plasma levels of lysosomal enzymes. Often fatal in childhood.



Signal recognition particle (SRP)

Abundant, cytosolic ribonucleoprotein that traffics proteins from the ribosome to the RER. Absent or dysfunctional SRP → proteins accumulate in the cytosol.

Vesicular trafficking proteins

COPI: Golgi → Golgi (retrograde); *cis*-Golgi → ER.

COPII: ER → *cis*-Golgi (anterograde).

"Two (COPII) steps forward (anterograde); one (COPI) step back (retrograde)."

Clathrin: *trans*-Golgi → lysosomes; plasma membrane → endosomes (receptor-mediated endocytosis [eg, LDL receptor activity]).

Peroxisome

Membrane-enclosed organelle involved in catabolism of very-long-chain fatty acids (through β-oxidation), branched-chain fatty acids, amino acids, and ethanol.

Peroxisomal disorders commonly lead to neurologic diseases due to deficits in synthesis of plasmalogens, important phospholipids in myelin. Peroxisomal diseases include Zellweger syndrome (hypotonia, seizures, hepatomegaly, early death) and Refsum disease (scaly skin, ataxia, cataracts/night blindness, shortening of 4th toe, epiphyseal dysplasia).

Proteasome

Barrel-shaped protein complex that degrades damaged or ubiquitin-tagged proteins. Defects in the ubiquitin-proteasome system have been implicated in some cases of Parkinson disease.

Cytoskeletal elements

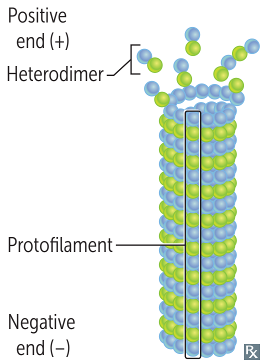
A network of protein fibers within the cytoplasm that supports cell structure, cell and organelle movement, and cell division.

TYPE OF FILAMENT	PREDOMINANT FUNCTION	EXAMPLES
Microfilaments	Muscle contraction, cytokinesis	Actin, microvilli.
Intermediate filaments	Maintain cell structure	Vimentin, desmin, cytokeratin, lamins, glial fibrillary acid proteins (GFAP), neurofilaments.
Microtubules	Movement, cell division	Cilia, flagella, mitotic spindle, axonal trafficking, centrioles.

Immunohistochemical stains for intermediate filaments

STAIN	CELL TYPE	IDENTIFIES
Vimentin	Mesenchymal tissue (eg, fibroblasts, endothelial cells, macrophages)	Mesenchymal tumors (eg, sarcoma), but also many other tumors (eg, endometrial carcinoma, renal cell carcinoma, meningioma)
DesMin	Muscle	Muscle tumors (eg, rhabdomyosarcoma)
Cytokeratin	Epithelial cells	Epithelial tumors (eg, squamous cell carcinoma)
GFAP	NeuroGlia (eg, astrocytes, Schwann cells, oligodendrocytes)	Astrocytoma, Glioblastoma
Neurofilaments	Neurons	Neuronal tumors (eg, neuroblastoma)

Microtubule



Cylindrical outer structure composed of a helical array of polymerized heterodimers of α- and β-tubulin. Each dimer has 2 GTP bound. Incorporated into flagella, cilia, mitotic spindles. Grows slowly, collapses quickly. Also involved in slow axoplasmic transport in neurons.

Molecular motor proteins—transport cellular cargo toward opposite ends of microtubule tracks.

- Dynein—retrograde to microtubule (+ → –).
- Kinesin—anterograde to microtubule (– → +).

Drugs that act on microtubules (Microtubules Get Constructed Very Poorly):

- Mebendazole (antihelminthic)
- Griseofulvin (antifungal)
- Colchicine (antigout)
- Vincristine/Vvinblastine (anticancer)
- Paclitaxel (anticancer)

Negative end Near Nucleus
Positive end Points to Periphery

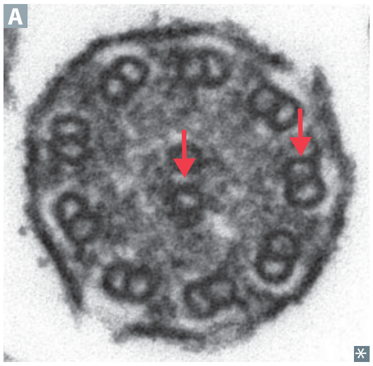
Cilia structure

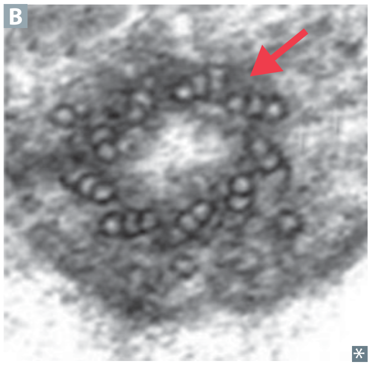
9 doublet + 2 singlet arrangement of microtubules (arrows in A).

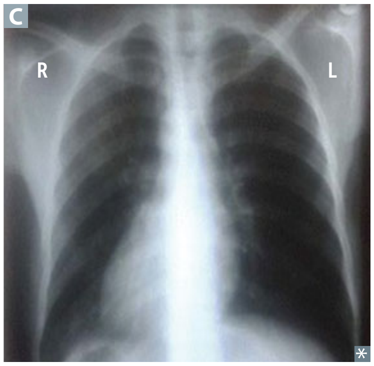
Basal body (base of cilium below cell membrane) consists of 9 microtubule triplets (arrow in B) with no central microtubules.

Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets.

Kartagener syndrome (1° ciliary dyskinesia)—immotile cilia due to a dynein arm defect. Results in ↓ male and female fertility due to immotile sperm and dysfunctional fallopian tube cilia, respectively; ↑ risk of ectopic pregnancy. Can cause bronchiectasis, recurrent sinusitis, chronic ear infections, conductive hearing loss, and situs inversus (eg, dextrocardia on CXR C).







Sodium-potassium pump

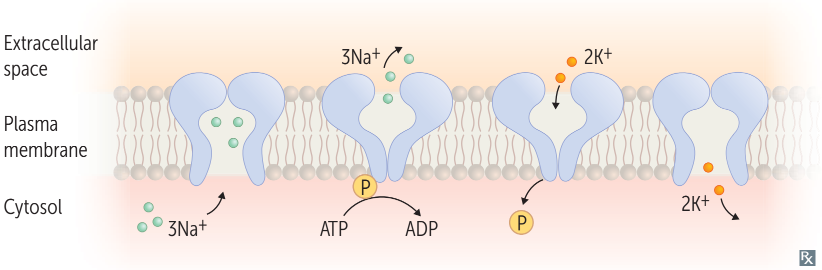
Na$^+$-K$^+$ ATPase is located in the plasma membrane with ATP site on cytosolic side. For each ATP consumed, 3Na$^+$ go out of the cell (pump phosphorylated) and 2K$^+$ come into the cell (pump dephosphorylated).

Plasma membrane is an asymmetric lipid bilayer containing cholesterol, phospholipids, sphingolipids, glycolipids, and proteins.

Pumpkin = pump K$^+$ in.

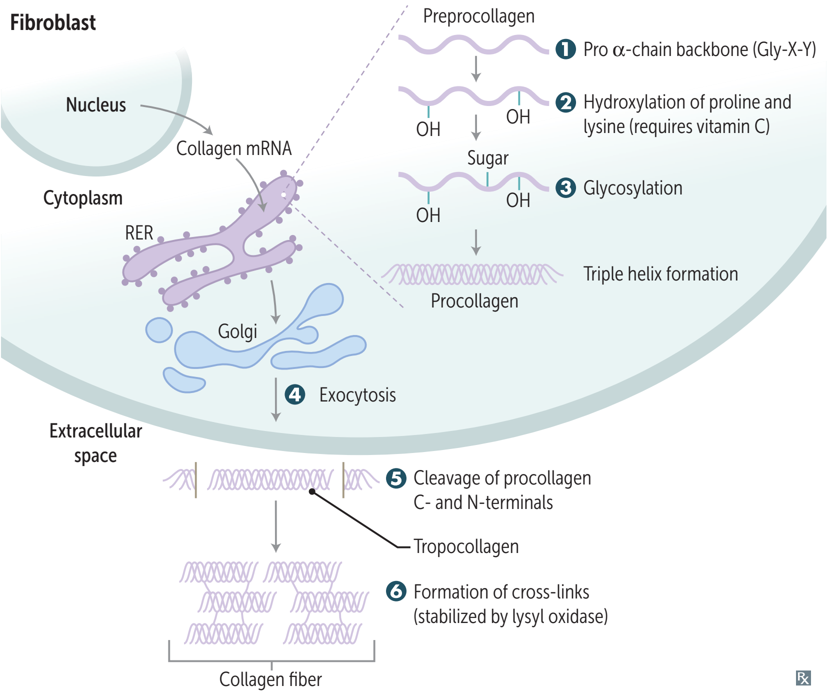
Ouabain inhibits by binding to K$^+$ site.

Cardiac glycosides (digoxin and digitoxin) directly inhibit the Na$^+$-K$^+$ ATPase, which leads to indirect inhibition of Na$^+$/Ca^{2+} exchange → ↑ [Ca^{2+}]$_i$ → ↑ cardiac contractility.



Collagen	Most abundant protein in the human body. Extensively modified by posttranslational modification. Organizes and strengthens extracellular matrix.	Be (So Totally) Cool, Read Books.
Type I	Most common (90%)—Bone (made by osteoblasts), Skin, Tendon, dentin, fascia, cornea, late wound repair.	Type I: bone. ↓ production in osteogenesis imperfecta type I.
Type II	Cartilage (including hyaline), vitreous body, nucleus pulposus.	Type II: cartwolage.
Type III	Reticulin—skin, **blood vessels**, uterus, fetal tissue, granulation tissue.	Type III: deficient in the uncommon, **vascular** type of Ehlers-Danlos syndrome (**ThreE D**).
Type IV	Basement membrane, basal lamina, lens.	Type IV: under the **floor** (basement membrane). Defective in Alport syndrome; targeted by autoantibodies in Goodpasture syndrome.

Collagen synthesis and structure


Fibroblast
Nucleus
Collagen mRNA
Cytoplasm
RER
Golgi
Preprocollagen
❶ Pro α-chain backbone (Gly-X-Y)
OH
OH
❷ Hydroxylation of proline and lysine (requires vitamin C)
Sugar
OH
OH
❸ Glycosylation
Triple helix formation
Procollagen
❹ Exocytosis
Extracellular space
❺ Cleavage of procollagen C- and N-terminals
Tropocollagen
❻ Formation of cross-links (stabilized by lysyl oxidase)
Collagen fiber

❶ Synthesis—translation of collagen α chains (preprocollagen)—usually Gly-X-Y (X and Y are proline or lysine). Glycine content best reflects collagen synthesis (collagen is ⅓ glycine).

❷ Hydroxylation—hydroxylation of specific proline and lysine residues. Requires vitamin C; deficiency → scurvy.

❸ Glycosylation—glycosylation of pro-α-chain hydroxylysine residues and formation of procollagen via hydrogen and disulfide bonds (triple helix of 3 collagen α chains). Problems forming triple helix → osteogenesis imperfecta.

❹ Exocytosis—exocytosis of procollagen into extracellular space.

❺ Proteolytic processing—cleavage of disulfide-rich terminal regions of procollagen → insoluble tropocollagen. Problems with cleavage → Ehlers-Danlos syndrome.

❻ Cross-linking—reinforcement of many staggered tropocollagen molecules by covalent lysine-hydroxylysine cross-linkage (by copper-containing lysyl oxidase) to make collagen fibrils. Problems with cross-linking → Ehlers-Danlos syndrome, Menkes disease.

Osteogenesis imperfecta

Genetic bone disorder (brittle bone disease) caused by a variety of gene defects (most commonly *COL1A1* and *COL1A2*).

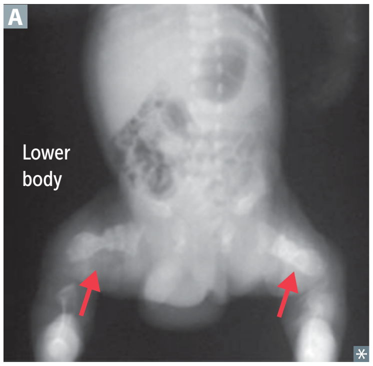
Most common form is autosomal dominant with ↓ production of otherwise normal type I collagen. Manifestations can include:

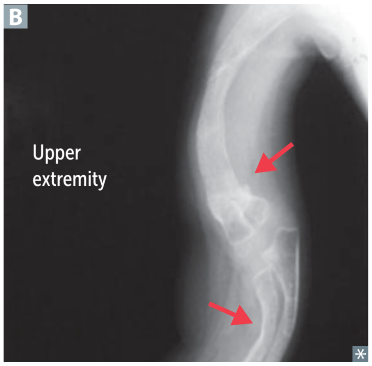
- Multiple fractures with minimal trauma A B; may occur during the birth process
- Blue sclerae C due to the translucent connective tissue over choroidal veins
- Some forms have tooth abnormalities, including opalescent teeth that wear easily due to lack of dentin (dentinogenesis imperfecta)
- Hearing loss (abnormal ossicles)

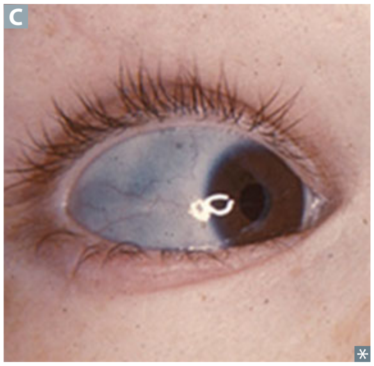
May be confused with child abuse.

Patients can't **BITE**:

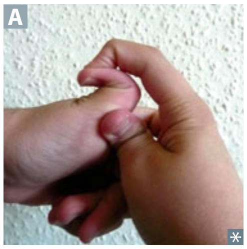
Bones = multiple fractures
I (eye) = blue sclerae
Teeth = dental imperfections
Ear = hearing loss







Ehlers-Danlos syndrome



Faulty collagen synthesis causing hyperextensible skin, tendency to bleed (easy bruising), and hypermobile joints A.

Multiple types. Inheritance and severity vary. Can be autosomal dominant or recessive. May be associated with joint dislocation, berry and aortic aneurysms, organ rupture.

Hypermobility type (joint instability): most common type.

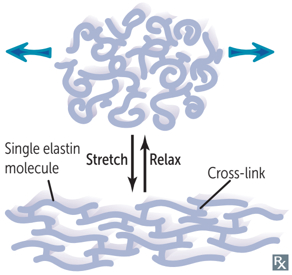
Classical type (joint and skin symptoms): caused by a mutation in type V collagen (eg, *COL5A1*, *COL5A2*).

Vascular type (vascular and organ rupture): deficient type III collagen.

Menkes disease

X-linked recessive connective tissue disease caused by impaired copper absorption and transport due to defective Menkes protein (ATP7A). Leads to ↓ activity of lysyl oxidase (copper is a necessary cofactor). Results in brittle, "kinky" hair, growth retardation, and hypotonia.

Elastin


Single elastin molecule
Stretch
Relax
Cross-link

Stretchy protein within skin, lungs, large arteries, elastic ligaments, vocal cords, ligamenta flava (connect vertebrae → relaxed and stretched conformations).

Rich in nonhydroxylated proline, glycine, and lysine residues.

Tropoelastin with fibrillin scaffolding.

Cross-linking takes place extracellularly and gives elastin its elastic properties.

Broken down by elastase, which is normally inhibited by α_1-antitrypsin.

α_1-Antitrypsin deficiency results in excess elastase activity, which can cause emphysema.

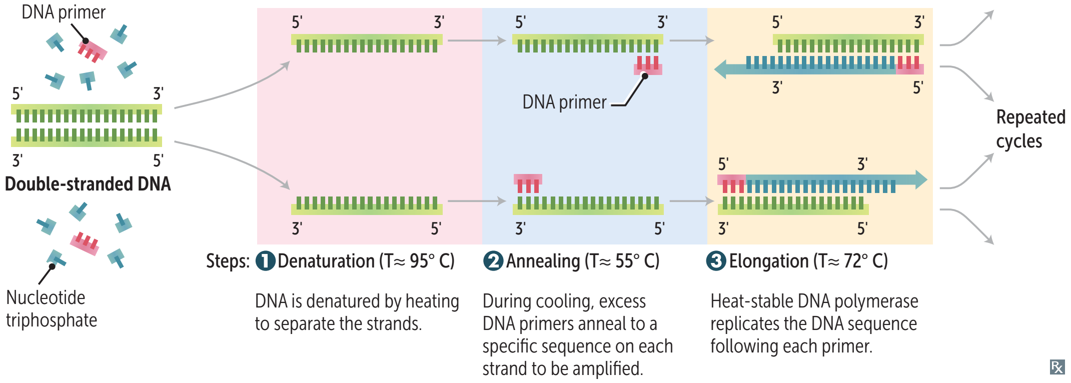
Wrinkles of aging are due to ↓ collagen and elastin production.

Marfan syndrome—autosomal dominant connective tissue disorder affecting skeleton, heart, and eyes. *FBN1* gene mutation on chromosome 15 results in defective fibrillin, a glycoprotein that forms a sheath around elastin. Findings: tall with long extremities; pectus carinatum (more specific) or pectus excavatum; hypermobile joints; long, tapering fingers and toes (arachnodactyly); cystic medial necrosis of aorta; aortic incompetence and dissecting aortic aneurysms; floppy mitral valve. Subluxation of lenses, typically upward and temporally.

▸ BIOCHEMISTRY—LABORATORY TECHNIQUES

Polymerase chain reaction

Molecular biology laboratory procedure used to amplify a desired fragment of DNA. Useful as a diagnostic tool (eg, neonatal HIV, herpes encephalitis).


DNA primer
5'
3'
3'
5'
Double-stranded DNA
Nucleotide triphosphate
5'
3'
3'
5'
DNA primer
Repeated cycles
Steps: ① Denaturation (T≈ 95° C)
② Annealing (T≈ 55° C)
③ Elongation (T≈ 72° C)

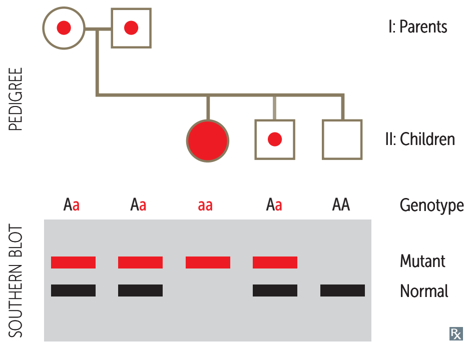
DNA is denatured by heating to separate the strands.

During cooling, excess DNA primers anneal to a specific sequence on each strand to be amplified.

Heat-stable DNA polymerase replicates the DNA sequence following each primer.

Blotting procedures

Southern blot	1. **DNA** sample is enzymatically cleaved into smaller pieces, which are separated on a gel by electrophoresis, and then transferred to a filter. 2. Filter is exposed to radiolabeled DNA probe that recognizes and anneals to its complementary strand. 3. Resulting double-stranded, labeled piece of DNA is visualized when filter is exposed to film.
Northern blot	Similar to Southern blot, except that an **RNA** sample is electrophoresed. Useful for studying mRNA levels, which are reflective of gene expression.
Western blot	Sample protein is separated via gel electrophoresis and transferred to a membrane. Labeled antibody is used to bind to relevant **protein** (eg, confirmatory test for HIV after ⊕ ELISA).
Southwestern blot	Identifies **DNA-binding proteins** (eg, transcription factors) using labeled oligonucleotide probes.



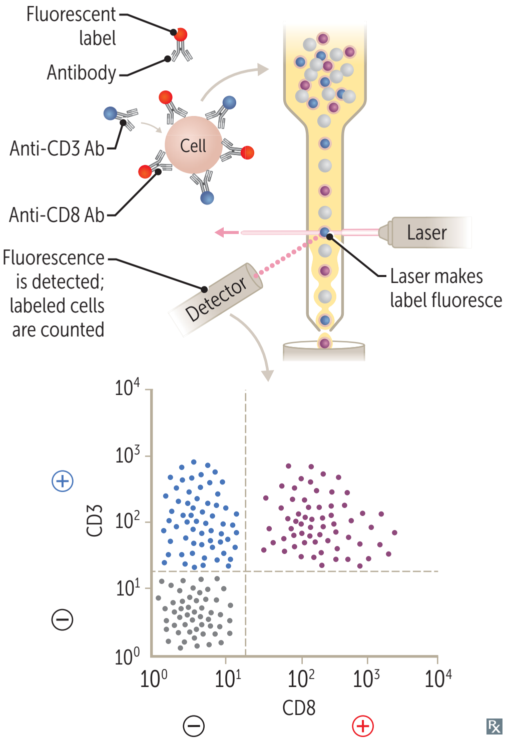
SNoW DRoP:
Southern = DNA
Northern = RNA
Western = Protein

Flow cytometry

Laboratory technique to assess size, granularity, and protein expression (immunophenotype) of individual cells in a sample.

Commonly used in workup of hematologic abnormalities (eg, paroxysmal nocturnal hemoglobinuria, fetal RBCs in mother's blood) and immunodeficiencies (eg, CD4 cell count in HIV).

Cells are tagged with antibodies specific to surface or intracellular proteins. Antibodies are then tagged with a unique fluorescent dye. Sample is analyzed one cell at a time by focusing a laser on the cell and measuring light scatter and intensity of fluorescence.


Fluorescent label
Antibody
Anti-CD3 Ab
Cell
Anti-CD8 Ab
Laser
Fluorescence is detected; labeled cells are counted
Detector
Laser makes label fluoresce
10^4
10^3
10^2
10^1
10^0
CD3
⊕
⊖
10^0
10^1
10^2
10^3
10^4
CD8
⊖
⊕

Data are plotted either as histogram (one measure) or scatter plot (any two measures, as shown). In illustration:

- Cells in left lower quadrant ⊖ for both CD8 and CD3.
- Cells in right lower quadrant ⊕ for CD8 and ⊖ for CD3. Right lower quadrant is empty because all CD8-expressing cells also express CD3.
- Cells in left upper quadrant ⊕ for CD3 and ⊖ for CD8.
- Cells in right upper quadrant ⊕ for CD8 and CD3 (red + blue → purple).

Microarrays

Thousands of nucleic acid sequences are arranged in grids on glass or silicon. DNA or RNA probes are hybridized to the chip, and a scanner detects the relative amounts of complementary binding.

Used to profile gene expression levels of thousands of genes simultaneously to study certain diseases and treatments. Able to detect single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) for a variety of applications including genotyping, clinical genetic testing, forensic analysis, cancer mutations, and genetic linkage analysis.

Enzyme-linked immunosorbent assay

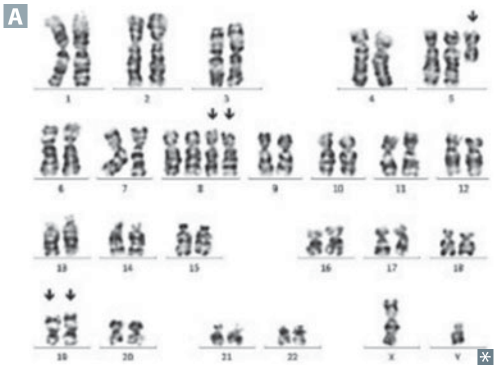
Immunologic test used to detect the presence of either a specific antigen (eg, HBsAg) or antibody (eg, anti-HBs) in a patient's blood sample. Detection involves the use of an antibody linked to an enzyme. Added substrate reacts with enzyme, producing a detectable signal. Can have high sensitivity and specificity, but is less specific than Western blot.

Karyotyping

A process in which metaphase chromosomes are stained, ordered, and numbered according to morphology, size, arm-length ratio, and banding pattern (arrows in A point to extensive abnormalities in a cancer cell).

Can be performed on a sample of blood, bone marrow, amniotic fluid, or placental tissue.

Used to diagnose chromosomal imbalances (eg, autosomal trisomies, sex chromosome disorders).

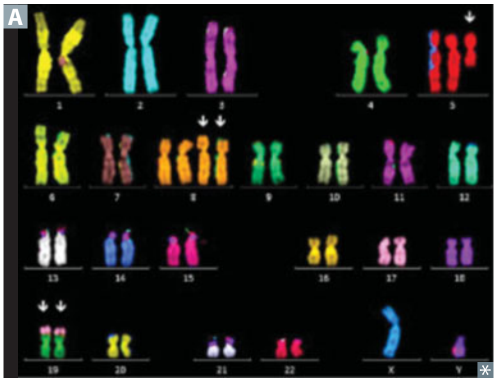


Fluorescence in situ hybridization

Fluorescent DNA or RNA probe binds to specific gene site of interest on chromosomes (arrows in A point to abnormalities in a cancer cell, whose karyotype is seen above; each fluorescent color represents a chromosome-specific probe).

Used for specific localization of genes and direct visualization of chromosomal anomalies at the molecular level.

- Microdeletion—no fluorescence on a chromosome compared to fluorescence at the same locus on the second copy of that chromosome
- Translocation—fluorescence signal that corresponds to one chromosome is found in a different chromosome
- Duplication—extra site of fluorescence on one chromosome relative to its homologous chromosome



Cloning methods

Cloning is the production of a recombinant DNA molecule that is self perpetuating.

Steps:

1. Isolate eukaryotic mRNA (post-RNA processing) of interest.
2. Expose mRNA to reverse transcriptase to produce cDNA (lacks introns).
3. Insert cDNA fragments into bacterial plasmids containing antibiotic resistance genes.
4. Transform recombinant plasmid into bacteria.
5. Surviving bacteria on antibiotic medium produce cloned DNA (copies of cDNA).

Gene expression modifications	Transgenic strategies in mice involve: ▪ Random insertion of gene into mouse genome ▪ Targeted insertion or deletion of gene through homologous recombination with mouse gene	Knock-**out** = removing a gene, taking it **out**. Knock-**in** = **in**serting a gene.
Cre-lox system	Can inducibly manipulate genes at specific developmental points (eg, to study a gene whose deletion causes embryonic death).	
RNA interference	dsRNA is synthesized that is complementary to the mRNA sequence of interest. When transfected into human cells, dsRNA separates and promotes degradation of target mRNA, "knocking down" gene expression.	

▸ BIOCHEMISTRY—GENETICS

Genetic terms

TERM	DEFINITION	EXAMPLE
Codominance	Both alleles contribute to the phenotype of the heterozygote.	Blood groups A, B, AB; α_1-antitrypsin deficiency.
Variable expressivity	Patients with the same genotype have varying phenotypes.	2 patients with neurofibromatosis type 1 (NF1) may have varying disease severity.
Incomplete penetrance	Not all individuals with a mutant genotype show the mutant phenotype.	*BRCA1* gene mutations do not always result in breast or ovarian cancer.
Pleiotropy	One gene contributes to multiple phenotypic effects.	Untreated phenylketonuria (PKU) manifests with light skin, intellectual disability, and musty body odor.
Anticipation	Increased severity or earlier onset of disease in succeeding generations.	Trinucleotide repeat diseases (eg, Huntington disease).
Loss of heterozygosity	If a patient inherits or develops a mutation in a tumor suppressor gene, the complementary allele must be deleted/mutated before cancer develops. This is not true of oncogenes.	Retinoblastoma and the "two-hit hypothesis," Lynch syndrome (HNPCC), Li-Fraumeni syndrome.
Dominant negative mutation	Exerts a dominant effect. A heterozygote produces a nonfunctional altered protein that also prevents the normal gene product from functioning.	Mutation of a transcription factor in its allosteric site. Nonfunctioning mutant can still bind DNA, preventing wild-type transcription factor from binding.
Linkage disequilibrium	Tendency for certain alleles at 2 linked loci to occur together more or less often than expected by chance. Measured in a population, not in a family, and often varies in different populations.	

Genetic terms *(continued)*

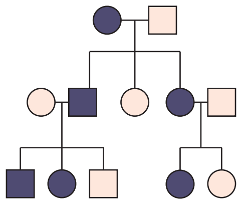
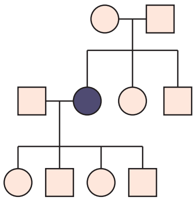
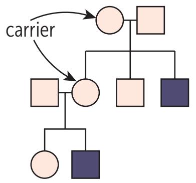
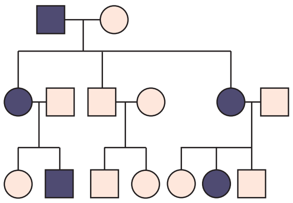
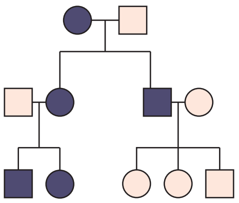
TERM	DEFINITION	EXAMPLE
Mosaicism	Presence of genetically distinct cell lines in the same individual. Somatic mosaicism—mutation arises from mitotic errors after fertilization and propagates through multiple tissues or organs. Gonadal mosaicism—mutation only in egg or sperm cells. If parents and relatives do not have the disease, suspect gonadal (or germline) mosaicism.	**McCune-Albright syndrome**—due to mutation affecting G-protein signaling. Presents with unilateral café-au-lait spots with ragged edges, polyostotic fibrous dysplasia, and at least one endocrinopathy (eg, precocious puberty). Lethal if mutation occurs before fertilization (affecting all cells), but survivable in patients with mosaicism.
Locus heterogeneity	Mutations at different loci can produce a similar phenotype.	Albinism.
Allelic heterogeneity	Different mutations in the same locus produce the same phenotype.	β-thalassemia.
Heteroplasmy	Presence of both normal and mutated mtDNA, resulting in variable expression in mitochondrially inherited disease.	
Uniparental disomy	Offspring receives 2 copies of a chromosome from 1 parent and no copies from the other parent. Heterod**I**somy (heterozygous) indicates a meiosis **I** error. **I**sod**I**somy (homozygous) indicates a meiosis **II** error or postzygotic chromosomal duplication of one of a pair of chromosomes, and loss of the other of the original pair.	Uniparental is euploid (correct number of chromosomes), not aneuploid. Most occurrences of uniparental disomy (UPD) → normal phenotype. Consider UPD in an individual manifesting a recessive disorder when only one parent is a carrier.

Hardy-Weinberg population genetics	If a population is in Hardy-Weinberg equilibrium and if p and q are the frequencies of separate alleles, then: $p^2 + 2pq + q^2 = 1$ and $p + q = 1$, which implies that: p^2 = frequency of homozygosity for allele A q^2 = frequency of homozygosity for allele a $2pq$ = frequency of heterozygosity (carrier frequency, if an autosomal recessive disease). The frequency of an X-linked recessive disease in males = q and in females = q^2.	Hardy-Weinberg law assumptions include: ▪ No mutation occurring at the locus ▪ Natural selection is not occurring ▪ Completely random mating ▪ No net migration

	pA	*qa*
pA	*AA* $p \times p = p^2$	*Aa* $p \times q$
qa	*Aa* $p \times q$	*aa* $q \times q = q^2$

Imprinting	At some loci, only one allele is active; the other is inactive (imprinted/inactivated by methylation). With one allele inactivated, deletion of the active allele → disease.	Both Prader-Willi and Angelman syndromes are due to mutation or deletion of genes on chromosome 15.
Prader-Willi syndrome	Maternal imprinting: gene from mom is normally silent and Paternal gene is deleted/mutated. Results in hyperphagia, obesity, intellectual disability, hypogonadism, and hypotonia.	25% of cases due to maternal uniparental disomy (two maternally imprinted genes are received; no paternal gene received).
AngelMan syndrome	Paternal imprinting: gene from dad is normally silent and Maternal gene is deleted/mutated. Results in inappropriate laughter ("happy puppet"), seizures, ataxia, and severe intellectual disability.	5% of cases due to paternal uniparental disomy (two paternally imprinted genes are received; no maternal gene received).

Modes of inheritance

Autosomal dominant 	Often due to defects in structural genes. Many generations, both males and females are affected.	Often pleiotropic (multiple apparently unrelated effects) and variably expressive (different between individuals). Family history crucial to diagnosis. With one affected (heterozygous) parent, on average, ½ of children affected.
Autosomal recessive 	Often due to enzyme deficiencies. Usually seen in only 1 generation.	Commonly more severe than dominant disorders; patients often present in childhood. ↑ risk in consanguineous families. With 2 carrier (heterozygous) parents, on average: ¼ of children will be affected (homozygous), ½ of children will be carriers, and ¼ of children will be neither affected nor carriers.
X-linked recessive 	Sons of heterozygous mothers have a 50% chance of being affected. No male-to-male transmission. Skips generations.	Commonly more severe in males. Females usually must be homozygous to be affected.
X-linked dominant 	Transmitted through both parents. Mothers transmit to 50% of daughters and sons; fathers transmit to all daughters but no sons.	**Hypophosphatemic rickets**—formerly known as vitamin D–resistant rickets. Inherited disorder resulting in ↑ phosphate wasting at proximal tubule. Results in rickets-like presentation. Other examples: fragile X syndrome, Alport syndrome.
Mitochondrial inheritance 	Transmitted only through the mother. All offspring of affected females may show signs of disease.	Variable expression in a population or even within a family due to heteroplasmy. **Mitochondrial myopathies**—rare disorders; often present with myopathy, lactic acidosis, and CNS disease, eg, MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes). 2° to failure in oxidative phosphorylation. Muscle biopsy often shows "ragged red fibers" (due to accumulation of diseased mitochondria).

□ = unaffected male; ■ = affected male; ○ = unaffected female; ● = affected female.

Autosomal dominant diseases

Achondroplasia, autosomal dominant polycystic kidney disease, familial adenomatous polyposis, familial hypercholesterolemia, hereditary hemorrhagic telangiectasia, hereditary spherocytosis, Huntington disease, Li-Fraumeni syndrome, Marfan syndrome, multiple endocrine neoplasias, neurofibromatosis type 1 (von Recklinghausen disease), neurofibromatosis type 2, tuberous sclerosis, von Hippel-Lindau disease.

Autosomal recessive diseases

Albinism, autosomal recessive polycystic kidney disease (ARPKD), cystic fibrosis, glycogen storage diseases, hemochromatosis, Kartagener syndrome, mucopolysaccharidoses (except Hunter syndrome), phenylketonuria, sickle cell anemia, sphingolipidoses (except Fabry disease), thalassemias, Wilson disease.

Cystic fibrosis

GENETICS	Autosomal recessive; defect in *CFTR* gene on chromosome 7; commonly a deletion of Phe508. Most common lethal genetic disease in Caucasian population.
PATHOPHYSIOLOGY	*CFTR* encodes an ATP-gated Cl^- channel that secretes Cl^- in lungs and GI tract, and reabsorbs Cl^- in sweat glands. Most common mutation → misfolded protein → protein retained in RER and not transported to cell membrane, causing ↓ Cl^- (and H_2O) secretion; ↑ intracellular Cl^- results in compensatory ↑ Na^+ reabsorption via epithelial Na^+ channels → ↑ H_2O reabsorption → abnormally thick mucus secreted into lungs and GI tract. ↑ Na^+ reabsorption also causes more negative transepithelial potential difference.
DIAGNOSIS	↑ Cl^- concentration (> 60 mEq/L) in sweat is diagnostic. Can present with contraction alkalosis and hypokalemia (ECF effects analogous to a patient taking a loop diuretic) because of ECF H_2O/Na^+ losses and concomitant renal K^+/H^+ wasting. ↑ immunoreactive trypsinogen (newborn screening).
COMPLICATIONS	Recurrent pulmonary infections (eg, *S aureus* [early infancy], *P aeruginosa* [adolescence]), chronic bronchitis and bronchiectasis → reticulonodular pattern on CXR, opacification of sinuses. Pancreatic insufficiency, malabsorption with steatorrhea, fat-soluble vitamin deficiencies (A, D, E, K), biliary cirrhosis, liver disease. Meconium ileus in newborns. Infertility in men (absence of vas deferens, spermatogenesis may be unaffected) and subfertility in women (amenorrhea, abnormally thick cervical mucus). Nasal polyps, clubbing of nails.
TREATMENT	Multifactorial: chest physiotherapy, albuterol, aerosolized dornase alfa (DNAse), and hypertonic saline facilitate mucus clearance. Azithromycin used as anti-inflammatory agent. Ibuprofen slows disease progression. Pancreatic enzymes for insufficiency.

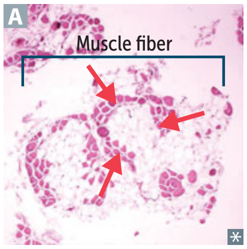
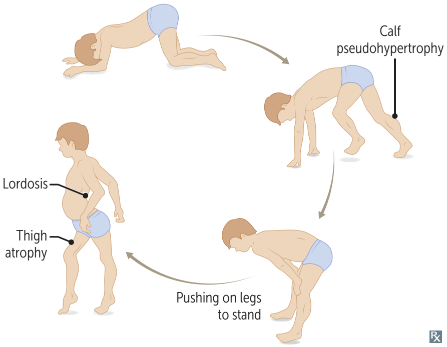
X-linked recessive disorders

Ornithine transcarbamylase deficiency, Fabry disease, Wiskott-Aldrich syndrome, Ocular albinism, G6PD deficiency, Hunter syndrome, Bruton agammaglobulinemia, Hemophilia A and B, Lesch-Nyhan syndrome, Duchenne (and Becker) muscular dystrophy.

Lyonization—female carriers variably affected depending on the pattern of inactivation of the X chromosome carrying the mutant vs normal gene.

Oblivious Female Will Often Give Her Boys Her x-Linked Disorders

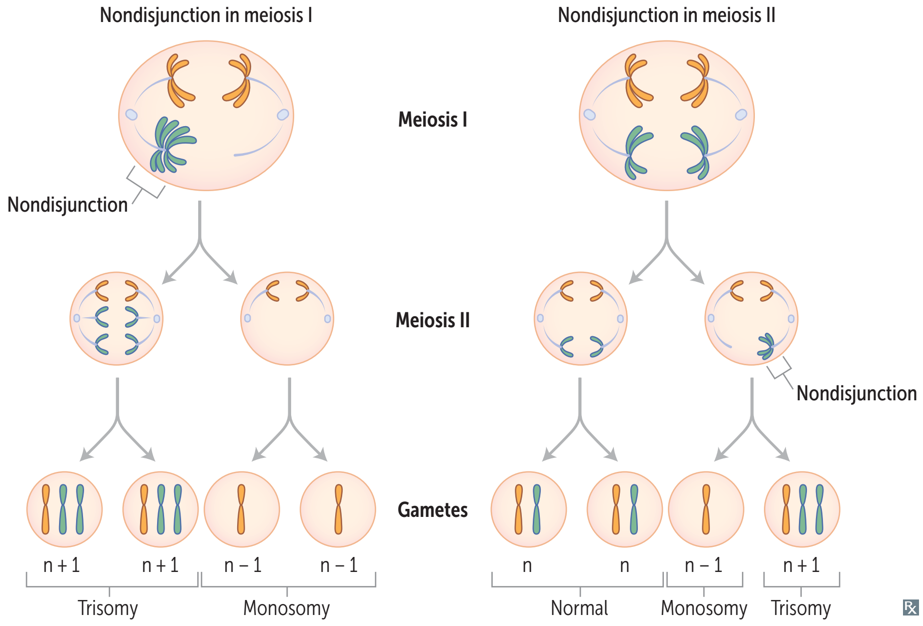
Muscular dystrophies

Duchenne 	X-linked disorder typically due to **frameshift** or nonsense mutations → truncated or absent dystrophin protein → progressive myofiber damage. Weakness begins in pelvic girdle muscles and progresses superiorly. Pseudohypertrophy of calf muscles due to fibrofatty replacement of muscle A. Waddling gait. Onset before 5 years of age. Dilated cardiomyopathy is common cause of death.	Duchenne = deleted dystrophin. Dystrophin gene (*DMD*) is the largest protein-coding human gene → ↑ chance of spontaneous mutation. Dystrophin helps anchor muscle fibers, primarily in skeletal and cardiac muscle. It connects the intracellular cytoskeleton (actin) to the transmembrane proteins α- and β-dystroglycan, which are connected to the extracellular matrix (ECM). Loss of dystrophin results in myonecrosis. ↑ CK and aldolase are seen; genetic testing confirms diagnosis.
Becker	X-linked disorder typically due to **non-frameshift** deletions in dystrophin gene (partially functional instead of truncated). Less severe than Duchenne. Onset in adolescence or early adulthood.	Deletions can cause both Duchenne and Becker muscular dystrophies. ⅔ of cases have large deletions spanning one or more exons.
Myotonic type 1	Autosomal dominant. CTG trinucleotide repeat expansion in the *DMPK* gene → abnormal expression of myotonin protein kinase → myotonia, muscle wasting, cataracts, testicular atrophy, frontal balding, arrhythmia.	Cataracts, Toupee (early balding in men), Gonadal atrophy.
	Gower sign—patient uses upper extremities to help stand up. Classically seen in Duchenne muscular dystrophy, but also seen in other muscular dystrophies and inflammatory myopathies (eg, polymyositis).	 Calf pseudohypertrophy Lordosis Thigh atrophy Pushing on legs to stand

Fragile X syndrome	X-linked dominant inheritance. Trinucleotide repeat in *FMR1* gene → hypermethylation → ↓ expression. Most common cause of inherited intellectual disability and autism and 2nd most common cause of genetically associated mental deficiency (after Down syndrome). Findings: post-pubertal macroorchidism (enlarged testes), long face with a large jaw, large everted ears, autism, mitral valve prolapse.	Trinucleotide repeat disorder (**CGG**)$_n$. **C**hin (protruding), **G**iant **G**onads
Trinucleotide repeat expansion diseases	**Hunting**ton disease, **my**otonic dystrophy, **fragile X** syndrome, and **Frie**dreich ataxia. May show genetic anticipation (disease severity ↑ and age of onset ↓ in successive generations).	**Try** (trinucleotide) **hunting** for **my fragile** cage-**free eggs** (X).
	Huntington disease = (**CAG**)$_n$	**C**audate has ↓ **A**Ch and **G**ABA
	Myotonic dystrophy = (**CTG**)$_n$	**C**ataracts, **T**oupee (early balding in men), **G**onadal atrophy
	Fragile X syndrome = (**CGG**)$_n$	**C**hin (protruding), **G**iant **G**onads
	Friedreich ataxia = (**GAA**)$_n$	Ataxic **GAA**it

Autosomal trisomies

Down syndrome (trisomy 21)	Findings: intellectual disability, flat facies, prominent epicanthal folds, single palmar crease, gap between 1st 2 toes, duodenal atresia, Hirschsprung disease, congenital heart disease (eg, atrioventricular septal defect), Brushfield spots. Associated with early-onset Alzheimer disease (chromosome 21 codes for amyloid precursor protein) and ↑ risk of ALL and AML. 95% of cases due to meiotic nondisjunction (↑ with advanced maternal age; from 1:1500 in women < 20 to 1:25 in women > 45 years old). 4% of cases due to unbalanced Robertsonian translocation, most typically between chromosomes 14 and 21. 1% of cases due to mosaicism (no association with maternal nondisjunction; postfertilization mitotic error).	Incidence 1:700. Drinking age (21). Most common viable chromosomal disorder and most common cause of genetic intellectual disability. First-trimester ultrasound commonly shows ↑ nuchal translucency and hypoplastic nasal bone; ↓ serum PAPP-A, ↑ free β-hCG. Second-trimester quad screen shows ↓ α-fetoprotein, ↑ β-hCG, ↓ estriol, ↑ inhibin A.
Edwards syndrome (trisomy 18)	Findings: PRINCE Edward—Prominent occiput, Rocker-bottom feet, Intellectual disability, Nondisjunction, Clenched fists (with overlapping fingers), low-set Ears, micrognathia (small jaw), congenital heart disease. Death usually occurs by age 1.	Incidence 1:8000. Election age (18). 2nd most common autosomal trisomy resulting in live birth (most common is Down syndrome). PAPP-A and free β-hCG are ↓ in first trimester. Quad screen shows ↓ α-fetoprotein, ↓ β-hCG, ↓ estriol, ↓ or normal inhibin A.
Patau syndrome (trisomy 13)	Findings: severe intellectual disability, rocker-bottom feet, microphthalmia, microcephaly, cleft liP/Palate, holoProsencephaly, Polydactyly, cutis aPlasia, congenital heart disease. Death usually occurs by age 1.	Incidence 1:15,000. Puberty (13). First-trimester pregnancy screen shows ↓ free β-hCG, ↓ PAPP-A.



Genetic disorders by chromosome

CHROMOSOME	SELECTED EXAMPLES
3	von Hippel-Lindau disease, renal cell carcinoma
4	ADPKD (*PKD2*), achondroplasia, Huntington disease
5	Cri-du-chat syndrome, familial adenomatous polyposis
6	Hemochromatosis (*HFE*)
7	Williams syndrome, cystic fibrosis
9	Friedreich ataxia
11	Wilms tumor, β-globin gene defects (eg, sickle cell disease, β-thalassemia, MEN1)
13	Patau syndrome, Wilson disease, retinoblastoma (*RB1*), *BRCA2*
15	Prader-Willi syndrome, Angelman syndrome, Marfan syndrome
16	ADPKD (*PKD1*), α-globin gene defects (eg, α-thalassemia)
17	Neurofibromatosis type 1, *BRCA1*, *p53*
18	Edwards syndrome
21	Down syndrome
22	Neurofibromatosis type 2, DiGeorge syndrome (22q11)
X	Fragile X syndrome, X-linked agammaglobulinemia, Klinefelter syndrome (XXY)

Robertsonian translocation

Chromosomal translocation that commonly involves chromosome pairs 13, 14, 15, 21, and 22. One of the most common types of translocation. Occurs when the long arms of 2 acrocentric chromosomes (chromosomes with centromeres near their ends) fuse at the centromere and the 2 short arms are lost. Balanced translocations normally do not cause any abnormal phenotype. Unbalanced translocations can result in miscarriage, stillbirth, and chromosomal imbalance (eg, Down syndrome, Patau syndrome).

Cri-du-chat syndrome

Congenital microdeletion of short arm of chromosome 5 (46,XX or XY, 5p–).

Findings: microcephaly, moderate to severe intellectual disability, high-pitched **cry**ing/**meow**ing, epicanthal folds, cardiac abnormalities (VSD).

Cri du chat = **cry** of the **cat**.

Williams syndrome

Congenital microdeletion of long arm of chromosome 7 (deleted region includes elastin gene).

Findings: distinctive "elfin" facies, intellectual disability, hypercalcemia (↑ sensitivity to vitamin D), well-developed verbal skills, extreme friendliness with strangers, cardiovascular problems.

22q11 deletion syndromes	Microdeletion at chromosome **22**q11 → variable presentations including **C**left palate, **A**bnormal facies, **T**hymic aplasia → T-cell deficiency, **C**ardiac defects, and **H**ypocalcemia 2° to parathyroid aplasia. DiGeorge syndrome—thymic, parathyroid, and cardiac defects. Velocardiofacial syndrome—palate, facial, and cardiac defects.	**CATCH-22**. Due to aberrant development of 3rd and 4th branchial pouches.

▸ BIOCHEMISTRY—NUTRITION

Vitamins: fat soluble	A, D, E, K. Absorption dependent on gut and pancreas. Toxicity more common than for water-soluble vitamins because fat-soluble vitamins accumulate in fat.	Malabsorption syndromes with steatorrhea, such as cystic fibrosis and celiac disease, or mineral oil intake can cause fat-soluble vitamin deficiencies.
Vitamins: water soluble	B_1 (thiamine: TPP) B_2 (riboflavin: FAD, FMN) B_3 (niacin: NAD^+) B_5 (pantothenic acid: CoA) B_6 (pyridoxine: PLP) B_7 (biotin) B_9 (folate) B_{12} (cobalamin) C (ascorbic acid)	All wash out easily from body except B_{12} and B_9 (folate). B_{12} stored in liver for ~ 3–4 years. B_9 stored in liver for ~ 3–4 months. B-complex deficiencies often result in dermatitis, glossitis, and diarrhea. Can be coenzymes (eg, ascorbic acid) or precursors to organic cofactors (eg, FAD, NAD^+).

Vitamin A (retinol)

FUNCTION	Antioxidant; constituent of visual pigments (**retina**l); essential for normal differentiation of epithelial cells into specialized tissue (pancreatic cells, mucus-secreting cells); prevents squamous metaplasia. Used to treat measles and acute promyelocytic leukemia (APL).	**Retin**ol is vitamin **A**, so think **retin-A** (used topically for wrinkles and **A**cne). Found in liver and leafy vegetables. Use oral isotretinoin to treat severe cystic acne. Use *all*-trans retinoic acid to treat acute promyelocytic leukemia.
DEFICIENCY	Night blindness (nyctalopia); dry, scaly skin (xerosis cutis); corneal degeneration (keratomalacia); Bitot spots on conjunctiva; immunosuppression.	
EXCESS	Acute toxicity—nausea, vomiting, vertigo, and blurred vision. Chronic toxicity—alopecia, dry skin (eg, scaliness), hepatic toxicity and enlargement, arthralgias, and pseudotumor cerebri. Teratogenic (cleft palate, cardiac abnormalities), therefore a ⊖ pregnancy test and two forms of contraception are required before isotretinoin (vitamin A derivative) is prescribed.	**Is**o**tret**inoin **is terat**ogenic.

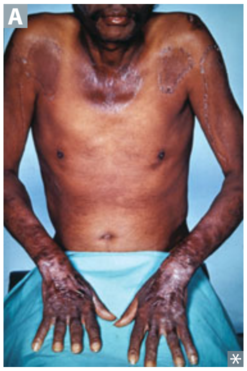
Vitamin B_1 (thiamine)

FUNCTION	In thiamine pyrophosphate (TPP), a cofactor for several dehydrogenase enzyme reactions: ▪ Pyruvate dehydrogenase (links glycolysis to TCA cycle) ▪ α-ketoglutarate dehydrogenase (TCA cycle) ▪ Transketolase (HMP shunt) ▪ Branched-chain ketoacid dehydrogenase	Think **ATP**: **α**-ketoglutarate dehydrogenase, **T**ransketolase, and **P**yruvate dehydrogenase. Spell beriberi as **Ber1Ber1** to remember vitamin **B_1**. **Wernicke-Korsakoff syndrome**—confusion, ophthalmoplegia, ataxia (classic triad) + confabulation, personality change, memory loss (permanent). Damage to medial dorsal nucleus of thalamus, mammillary bodies. **Dry beriberi**—polyneuritis, symmetrical muscle wasting. **Wet beriberi**—high-output cardiac failure (dilated cardiomyopathy), edema.
DEFICIENCY	Impaired glucose breakdown → ATP depletion worsened by glucose infusion; highly aerobic tissues (eg, brain, heart) are affected first. In alcoholic or malnourished patients, give thiamine before dextrose to ↓ risk of precipitating Wernicke encephalopathy. Diagnosis made by ↑ in RBC transketolase activity following vitamin B_1 administration.	

Vitamin B_2 (riboflavin)

FUNCTION	Component of flavins FAD and FMN, used as cofactors in redox reactions, eg, the succinate dehydrogenase reaction in the TCA cycle.	FAD and FMN are derived from riboFlavin ($B_2 \approx 2$ ATP).
DEFICIENCY	Cheilosis (inflammation of lips, scaling and fissures at the corners of the mouth), Corneal vascularization.	The 2 C's of B_2.

Vitamin B_3 (niacin)

FUNCTION	Constituent of NAD^+, $NADP^+$ (used in redox reactions). Derived from tryptophan. Synthesis requires vitamins B_2 and B_6. Used to treat dyslipidemia; lowers levels of VLDL and raises levels of HDL.	NAD derived from Niacin ($B_3 \approx 3$ ATP).
DEFICIENCY  	Glossitis. Severe deficiency leads to pellagra, which can be caused by Hartnup disease, malignant carcinoid syndrome (↑ tryptophan metabolism), and isoniazid (↓ vitamin B_6). Symptoms of pellagra: Diarrhea, Dementia (also hallucinations), Dermatitis (C3/C4 dermatome circumferential "broad collar" rash [Casal necklace], hyperpigmentation of sun-exposed limbs A).	The 3 D's of B_3. **Hartnup disease**—autosomal recessive. Deficiency of neutral amino acid (eg, tryptophan) transporters in proximal renal tubular cells and on enterocytes → neutral aminoaciduria and ↓ absorption from the gut → ↓ tryptophan for conversion to niacin → pellagra-like symptoms. Treat with high-protein diet and nicotinic acid.
EXCESS	Facial flushing (induced by prostaglandin, not histamine; can avoid by taking aspirin with niacin), hyperglycemia, hyperuricemia.	

Vitamin B_5 (pantothenic acid)

FUNCTION	Essential component of coenzyme A (CoA, a cofactor for acyl transfers) and fatty acid synthase.	B_5 is "pento"thenic acid.
DEFICIENCY	Dermatitis, enteritis, alopecia, adrenal insufficiency.	

Vitamin B_6 (pyridoxine)

FUNCTION	Converted to pyridoxal phosphate (PLP), a cofactor used in transamination (eg, ALT and AST), decarboxylation reactions, glycogen phosphorylase. Synthesis of cystathionine, heme, niacin, histamine, and neurotransmitters including serotonin, epinephrine, norepinephrine (NE), dopamine, and GABA.
DEFICIENCY	Convulsions, hyperirritability, peripheral neuropathy (deficiency inducible by isoniazid and oral contraceptives), sideroblastic anemias due to impaired hemoglobin synthesis and iron excess.

Vitamin B_7 (biotin)

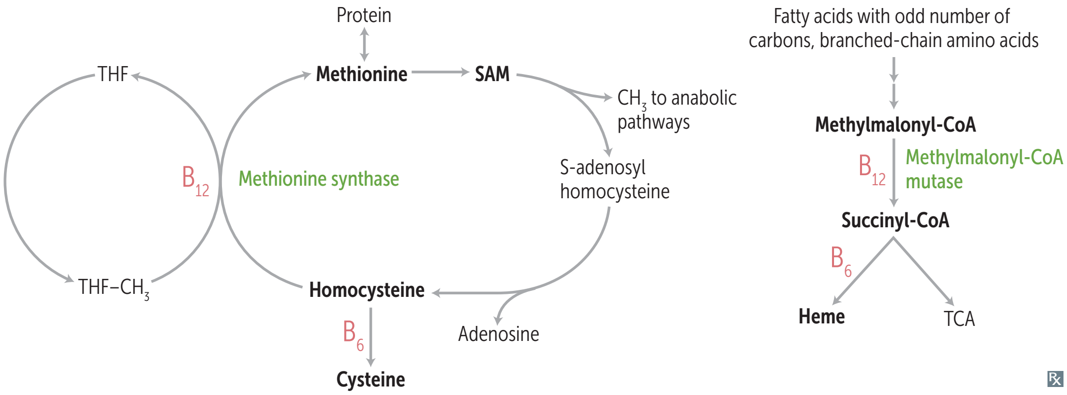
FUNCTION	Cofactor for carboxylation enzymes (which add a 1-carbon group): ▪ Pyruvate carboxylase: pyruvate (3C) → oxaloacetate (4C) ▪ Acetyl-CoA carboxylase: acetyl-CoA (2C) → malonyl-CoA (3C) ▪ Propionyl-CoA carboxylase: propionyl-CoA (3C) → methylmalonyl-CoA (4C)	"**Avid**in in egg whites **avid**ly binds biotin."
DEFICIENCY	Relatively rare. Dermatitis, alopecia, enteritis. Caused by antibiotic use or excessive ingestion of raw egg whites.	

Vitamin B_9 (folate)

FUNCTION	Converted to tetrahydrofolic acid (THF), a coenzyme for 1-carbon transfer/methylation reactions. Important for the synthesis of nitrogenous bases in DNA and RNA.	Found in leafy green vegetables. Absorbed in jejunum. **Fol**ate from **fol**iage. Small reserve pool stored primarily in the liver.
DEFICIENCY	Macrocytic, megaloblastic anemia; hypersegmented polymorphonuclear cells (PMNs); glossitis; no neurologic symptoms (as opposed to vitamin B_{12} deficiency). Labs: ↑ homocysteine, normal methylmalonic acid levels. Most common vitamin deficiency in the United States. Seen in alcoholism and pregnancy.	Deficiency can be caused by several drugs (eg, phenytoin, sulfonamides, methotrexate). Supplemental maternal folic acid at least 1 month prior to conception and during early pregnancy to ↓ risk of neural tube defects.

Vitamin B_{12} (cobalamin)

FUNCTION	Cofactor for methionine synthase (transfers CH_3 groups as methylcobalamin) and methylmalonyl-CoA mutase. Important for DNA synthesis.	Found in animal products. Synthesized only by microorganisms. Very large reserve pool (several years) stored primarily in the liver. Deficiency caused by malabsorption (eg, sprue, enteritis, *Diphyllobothrium latum*), lack of intrinsic factor (pernicious anemia, gastric bypass surgery), absence of terminal ileum (surgical resection, eg, for Crohn disease), or insufficient intake (eg, veganism). Anti-intrinsic factor antibodies diagnostic for pernicious anemia.
DEFICIENCY	Macrocytic, megaloblastic anemia; hypersegmented PMNs; paresthesias and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin. Associated with ↑ serum homocysteine and methylmalonic acid levels, along with 2° folate deficiency. Prolonged deficiency → irreversible nerve damage.	

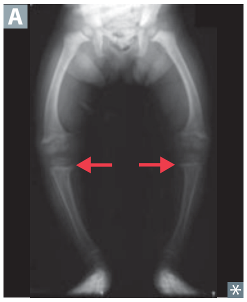

Protein
THF
Methionine
SAM
CH_3 to anabolic pathways
B_{12}
Methionine synthase
S-adenosyl homocysteine
THF–CH_3
Homocysteine
B_6
Adenosine
Cysteine
Fatty acids with odd number of carbons, branched-chain amino acids
Methylmalonyl-CoA
B_{12}
Methylmalonyl-CoA mutase
Succinyl-CoA
B_6
Heme
TCA

Vitamin C (ascorbic acid)

FUNCTION	Antioxidant; also facilitates iron absorption by reducing it to Fe^{2+} state. Necessary for hydroxylation of proline and lysine in collagen synthesis. Necessary for dopamine β-hydroxylase, which converts dopamine to NE.	Found in fruits and vegetables. Pronounce "**absorb**ic" acid. Ancillary treatment for methemoglobinemia by reducing Fe^{3+} to Fe^{2+}.
DEFICIENCY	**Scurvy**—swollen gums, bruising, petechiae, hemarthrosis, anemia, poor wound healing, perifollicular and subperiosteal hemorrhages, "corkscrew" hair. Weakened immune response.	Vitamin **C** deficiency causes s**C**urvy due to a **C**ollagen synthesis defect.
EXCESS	Nausea, vomiting, diarrhea, fatigue, calcium oxalate nephrolithiasis. Can ↑ risk of iron toxicity in predisposed individuals (eg, those with transfusions, hereditary hemochromatosis).	

Vitamin D

D_2 = ergocalciferol—ingested from plants.
D_3 = cholecalciferol—consumed in milk, formed in sun-exposed skin (stratum basale).
25-OH D_3 = storage form.
1,25-$(OH)_2$ D_3 (calcitriol) = active form.

FUNCTION	↑ intestinal absorption of calcium and phosphate, ↑ bone mineralization at low levels, ↑ bone resorption at higher levels.
DEFICIENCY 	Rickets in children (deformity, such as genu varum “bow legs” A), osteomalacia in adults (bone pain and muscle weakness), hypocalcemic tetany. Breastfed infants should receive oral vitamin D. Deficiency is exacerbated by low sun exposure, pigmented skin, prematurity.
EXCESS	Hypercalcemia, hypercalciuria, loss of appetite, stupor. Seen in granulomatous disease (↑ activation of vitamin D by epithelioid macrophages).

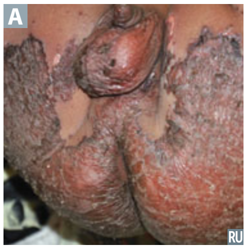
Vitamin E (tocopherol/tocotrienol)

FUNCTION	Antioxidant (protects RBCs and membranes from free radical damage).	High-dose supplementation may alter metabolism of vitamin K → enhanced anticoagulant effects of warfarin.
DEFICIENCY	Hemolytic anemia, acanthocytosis, muscle weakness, posterior column and spinocerebellar tract demyelination.	Neurologic presentation may appear similar to vitamin B_{12} deficiency, but without megaloblastic anemia, hypersegmented neutrophils, or ↑ serum methylmalonic acid levels.

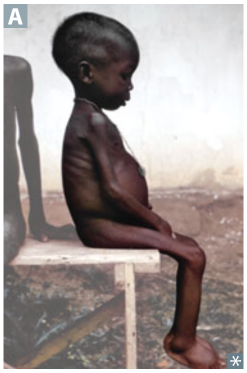
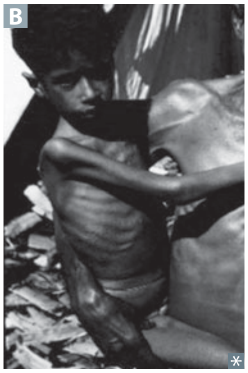
Vitamin K (phytomenadione, phylloquinone, phytonadione)

FUNCTION	Activated by epoxide reductase to the reduced form, which is a cofactor for the γ-carboxylation of glutamic acid residues on various proteins required for blood clotting. Synthesized by intestinal flora.	**K** is for **K**oagulation. Necessary for the maturation of clotting factors II, VII, IX, X, and proteins C and S. Warfarin inhibits vitamin K–dependent synthesis of these factors and proteins.
DEFICIENCY	Neonatal hemorrhage with ↑ PT and ↑ aPTT but normal bleeding time (neonates have sterile intestines and are unable to synthesize vitamin K). Can also occur after prolonged use of broad-spectrum antibiotics.	Not in breast milk; neonates are given vitamin K injection at birth to prevent hemorrhagic disease of the newborn.

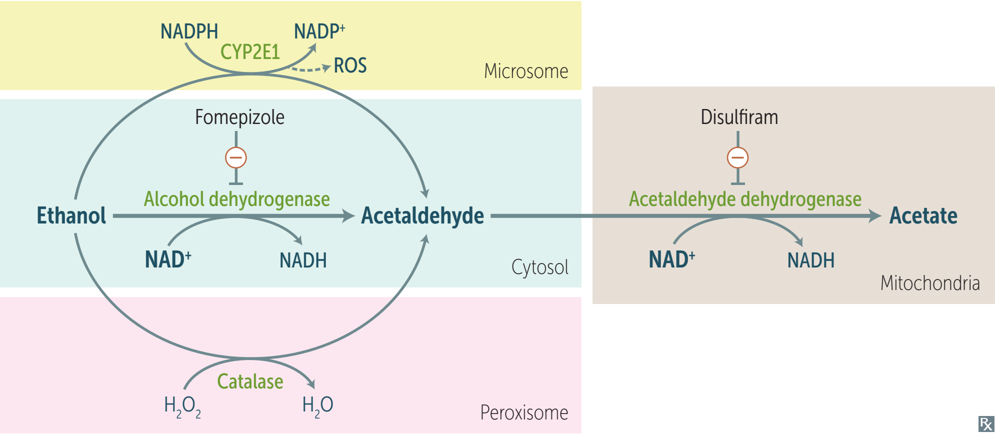
Zinc

FUNCTION	Mineral essential for the activity of 100+ enzymes. Important in the formation of zinc fingers (transcription factor motif).
DEFICIENCY 	Delayed wound healing, hypogonadism, ↓ adult hair (axillary, facial, pubic), dysgeusia, anosmia, acrodermatitis enteropathica A. May predispose to alcoholic cirrhosis.

Protein-energy malnutrition

Kwashiorkor	Protein malnutrition resulting in skin lesions, edema due to ↓ plasma oncotic pressure, liver malfunction (fatty change due to ↓ apolipoprotein synthesis). Clinical picture is small child with swollen abdomen A. Kwashiorkor results from protein-deficient **MEALS**: **M**alnutrition **E**dema **A**nemia **L**iver (fatty) **S**kin lesions (hyperkeratosis/hyperpigmentation)	 
Marasmus	Malnutrition not causing edema. Diet is deficient in calories but no nutrients are entirely absent. **M**arasmus results in **M**uscle wasting B.	

Ethanol metabolism


NADPH
NADP+
CYP2E1
ROS
Microsome
Fomepizole
Ethanol
Alcohol dehydrogenase
Acetaldehyde
NAD+
NADH
Cytosol
Disulfiram
Acetaldehyde dehydrogenase
Acetate
NAD+
NADH
Mitochondria
Catalase
H2O2
H2O
Peroxisome

FOMEpizole—inhibits alcohol dehydrogenase and is an antidote For Overdoses of Methanol or Ethylene glycol.

Disulfiram—inhibits acetaldehyde dehydrogenase (acetaldehyde accumulates, contributing to hangover symptoms), discouraging drinking.

NAD$^+$ is the limiting reagent.

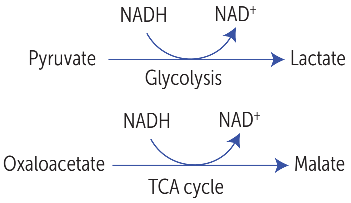
Alcohol dehydrogenase operates via zero-order kinetics.

Ethanol metabolism ↑ NADH/NAD$^+$ ratio in liver, causing:

- Pyruvate → lactate (lactic acidosis)
- Oxaloacetate → malate (prevents gluconeogenesis → fasting hypoglycemia)
- Dihydroxyacetone phosphate → glycerol-3-phosphate (combines with fatty acids to make triglycerides → hepatosteatosis)

End result is clinical picture seen in chronic alcoholism.

Additionally, ↑ NADH/NAD$^+$ ratio disfavors TCA production of NADH → ↑ utilization of acetyl-CoA for ketogenesis (→ ketoacidosis) and lipogenesis (→ hepatosteatosis).


NADH
NAD+
Pyruvate
Lactate
Glycolysis
NADH
NAD+
Oxaloacetate
Malate
TCA cycle

▸ BIOCHEMISTRY—METABOLISM

Metabolism sites

Mitochondria	Fatty acid oxidation (β-oxidation), acetyl-CoA production, TCA cycle, oxidative phosphorylation, ketogenesis.	
Cytoplasm	Glycolysis, HMP shunt, and synthesis of steroids (SER), proteins (ribosomes, RER), fatty acids, cholesterol, and nucleotides.	
Both	Heme synthesis, Urea cycle, Gluconeogenesis.	HUGs take two (ie, both).

Enzyme terminology

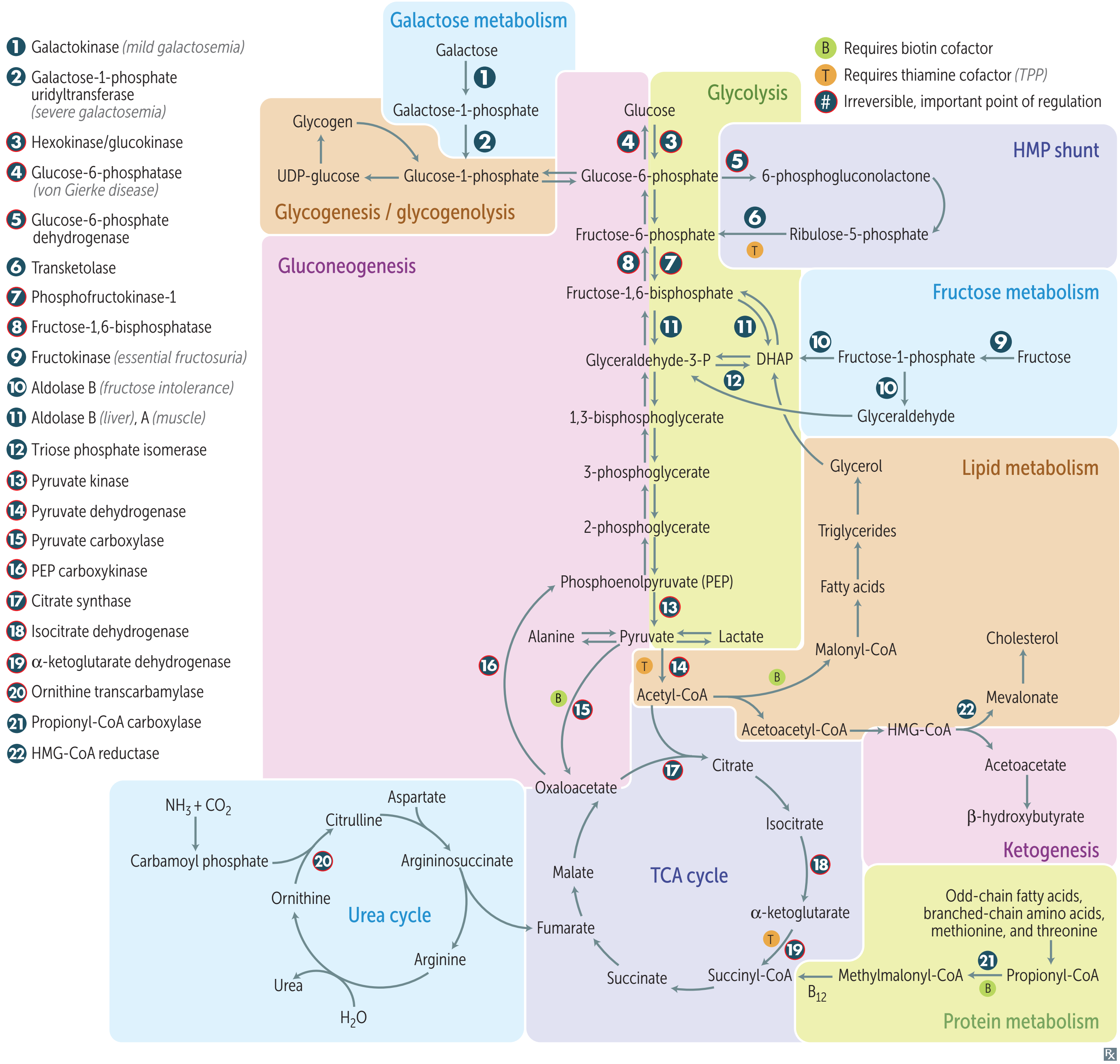
An enzyme's name often describes its function. For example, glucokinase is an enzyme that catalyzes the phosphorylation of glucose using a molecule of ATP. The following are commonly used enzyme descriptors.

Kinase	Catalyzes transfer of a phosphate group from a high-energy molecule (usually ATP) to a substrate (eg, phosphofructokinase).
Phosphorylase	Adds inorganic phosphate onto substrate without using ATP (eg, glycogen phosphorylase).
Phosphatase	Removes phosphate group from substrate (eg, fructose-1,6-bisphosphatase).
Dehydrogenase	Catalyzes oxidation-reduction reactions (eg, pyruvate dehydrogenase).
Hydroxylase	Adds hydroxyl group (−OH) onto substrate (eg, tyrosine hydroxylase).
Carboxylase	Transfers CO_2 groups with the help of biotin (eg, pyruvate carboxylase).
Mutase	Relocates a functional group within a molecule (eg, vitamin B_{12}–dependent methylmalonyl-CoA mutase).
Synthase/synthetase	Combines 2 molecules into 1 (condensation reaction) either using an energy source (synthase, eg, glycogen synthase) or not (synthetase, eg, PRPP synthetase).

Rate-determining enzymes of metabolic processes

PROCESS	ENZYME	REGULATORS
Glycolysis	Phosphofructokinase-1 (PFK-1)	AMP ⊕, fructose-2,6-bisphosphate ⊕ ATP ⊖, citrate ⊖
Gluconeogenesis	Fructose-1,6-bisphosphatase	Citrate ⊕ AMP ⊖, fructose-2,6-bisphosphate ⊖
TCA cycle	Isocitrate dehydrogenase	ADP ⊕ ATP ⊖, NADH ⊖
Glycogenesis	Glycogen synthase	Glucose-6-phosphate ⊕, insulin ⊕, cortisol ⊕ Epinephrine ⊖, glucagon ⊖
Glycogenolysis	Glycogen phosphorylase	Epinephrine ⊕, glucagon ⊕, AMP ⊕ Glucose-6-phosphate ⊖, insulin ⊖, ATP ⊖
HMP shunt	Glucose-6-phosphate dehydrogenase (G6PD)	$NADP^+$ ⊕ NADPH ⊖
De novo pyrimidine synthesis	Carbamoyl phosphate synthetase II	ATP ⊕, PRPP ⊕ UTP ⊖
De novo purine synthesis	Glutamine-phosphoribosylpyrophosphate (PRPP) amidotransferase	AMP ⊖, inosine monophosphate (IMP) ⊖, GMP ⊖
Urea cycle	Carbamoyl phosphate synthetase I	N-acetylglutamate ⊕
Fatty acid synthesis	Acetyl-CoA carboxylase (ACC)	Insulin ⊕, citrate ⊕ Glucagon ⊖, palmitoyl-CoA ⊖
Fatty acid oxidation	Carnitine acyltransferase I	Malonyl-CoA ⊖
Ketogenesis	HMG-CoA synthase	
Cholesterol synthesis	HMG-CoA reductase	Insulin ⊕, thyroxine ⊕ Glucagon ⊖, cholesterol ⊖

Summary of pathways



① Galactokinase *(mild galactosemia)*

② Galactose-1-phosphate uridyltransferase *(severe galactosemia)*

③ Hexokinase/glucokinase

④ Glucose-6-phosphatase *(von Gierke disease)*

⑤ Glucose-6-phosphate dehydrogenase

⑥ Transketolase

⑦ Phosphofructokinase-1

⑧ Fructose-1,6-bisphosphatase

⑨ Fructokinase *(essential fructosuria)*

⑩ Aldolase B *(fructose intolerance)*

⑪ Aldolase B *(liver)*, A *(muscle)*

⑫ Triose phosphate isomerase

⑬ Pyruvate kinase

⑭ Pyruvate dehydrogenase

⑮ Pyruvate carboxylase

⑯ PEP carboxykinase

⑰ Citrate synthase

⑱ Isocitrate dehydrogenase

⑲ α-ketoglutarate dehydrogenase

⑳ Ornithine transcarbamylase

㉑ Propionyl-CoA carboxylase

㉒ HMG-CoA reductase

B Requires biotin cofactor

T Requires thiamine cofactor *(TPP)*

# Irreversible, important point of regulation

Galactose metabolism
Galactose
①
Galactose-1-phosphate
②
Glycogen
UDP-glucose
Glucose-1-phosphate
Glycogenesis / glycogenolysis
Glycolysis
Glucose
④
③
Glucose-6-phosphate
⑤
6-phosphogluconolactone
HMP shunt
⑥
Ribulose-5-phosphate
T
Fructose-6-phosphate
Gluconeogenesis
⑧
⑦
Fructose-1,6-bisphosphate
Fructose metabolism
⑪
⑪
Glyceraldehyde-3-P
DHAP
⑩
Fructose-1-phosphate
⑨
Fructose
⑫
⑩
Glyceraldehyde
1,3-bisphosphoglycerate
Glycerol
Lipid metabolism
3-phosphoglycerate
Triglycerides
2-phosphoglycerate
Fatty acids
Phosphoenolpyruvate (PEP)
⑬
Alanine
Pyruvate
Lactate
Malonyl-CoA
Cholesterol
⑯
T
⑭
B
B
⑮
Acetyl-CoA
㉒
Mevalonate
Acetoacetyl-CoA
HMG-CoA
Acetoacetate
β-hydroxybutyrate
Ketogenesis
Oxaloacetate
⑰
Citrate
NH₃ + CO₂
Aspartate
Citrulline
Carbamoyl phosphate
⑳
Argininosuccinate
Ornithine
Urea cycle
Arginine
Urea
H₂O
Isocitrate
⑱
Malate
TCA cycle
Fumarate
α-ketoglutarate
T
⑲
Succinate
Succinyl-CoA
Methylmalonyl-CoA
B₁₂
㉑
B
Propionyl-CoA
Odd-chain fatty acids, branched-chain amino acids, methionine, and threonine
Protein metabolism

ATP production

Aerobic metabolism of glucose produces 32 net ATP via malate-aspartate shuttle (heart and liver), 30 net ATP via glycerol-3-phosphate shuttle (muscle).

Anaerobic glycolysis produces only 2 net ATP per glucose molecule.

ATP hydrolysis can be coupled to energetically unfavorable reactions.

Arsenic causes glycolysis to produce zero net ATP.

Activated carriers

CARRIER MOLECULE	CARRIED IN ACTIVATED FORM
ATP	Phosphoryl groups
NADH, NADPH, $FADH_2$	Electrons
CoA, lipoamide	Acyl groups
Biotin	CO_2
Tetrahydrofolates	1-carbon units
S-adenosylmethionine (SAM)	CH_3 groups
TPP	Aldehydes

Universal electron acceptors

Nicotinamides (NAD^+ from vitamin B_3, $NADP^+$) and flavin nucleotides (FAD^+ from vitamin B_2).

NAD^+ is generally used in **catabolic** processes to carry reducing equivalents away as NADH.

NADPH is used in **anabolic** processes (steroid and fatty acid synthesis) as a supply of reducing equivalents.

NADPH is a product of the HMP shunt.

NADPH is used in:

- Anabolic processes
- Respiratory burst
- Cytochrome P-450 system
- Glutathione reductase

Hexokinase vs glucokinase

Phosphorylation of glucose to yield glucose-6-phosphate serves as the 1st committed step of glycolysis (also serves as the 1st step of glycogen synthesis in the liver). Reaction is catalyzed by either hexokinase or glucokinase, depending on the tissue. At low glucose concentrations, hexokinase sequesters glucose in the tissue. At high glucose concentrations, excess glucose is stored in the liver.

	Hexokinase	**Glucokinase**
Location	Most tissues, except liver and pancreatic β cells	Liver, β cells of pancreas
K_m	Lower (↑ affinity)	Higher (↓ affinity)
V_{max}	Lower (↓ capacity)	Higher (↑ capacity)
Induced by insulin	No	Yes
Feedback-inhibited by glucose-6-phosphate	Yes	No

Glycolysis regulation, key enzymes

Net glycolysis (cytoplasm):
Glucose + 2 P_i + 2 ADP + 2 NAD^+ → 2 pyruvate + 2 ATP + 2 NADH + 2 H^+ + 2 H_2O.

Equation not balanced chemically, and exact balanced equation depends on ionization state of reactants and products.

REQUIRE ATP

$$\text{Glucose} \xrightarrow[\text{Hexokinase/glucokinase}^{a}]{} \text{Glucose-6-P}$$

Glucose-6-P ⊖ hexokinase.
Fructose-6-P ⊖ glucokinase.

$$\text{Fructose-6-P} \xrightarrow[\substack{\text{Phosphofructokinase-1} \\ \text{(rate-limiting step)}}]{} \text{Fructose-1,6-BP}$$

AMP ⊕, fructose-2,6-bisphosphate ⊕.
ATP ⊖, citrate ⊖.

[a] Glucokinase in liver and β cells of pancreas; hexokinase in all other tissues.

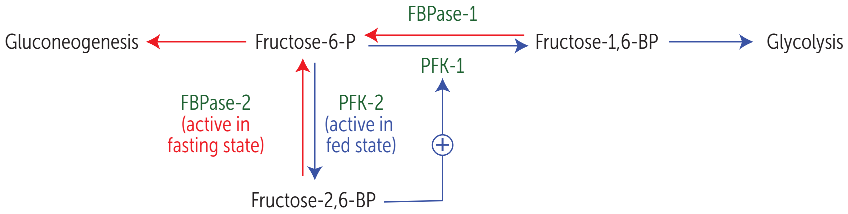
PRODUCE ATP

$$\text{1,3-BPG} \xrightleftharpoons[\text{Phosphoglycerate kinase}]{} \text{3-PG}$$

$$\text{Phosphoenolpyruvate} \xrightarrow[\text{Pyruvate kinase}]{} \text{Pyruvate}$$

Fructose-1,6-bisphosphate ⊕.
ATP ⊖, alanine ⊖.

Regulation by fructose-2,6-bisphosphate



FBPase-2 (fructose bisphosphatase-2) and PFK-2 (phosphofructokinase-2) are the same bifunctional enzyme whose function is reversed by phosphorylation by protein kinase A.

Fasting state: ↑ glucagon → ↑ cAMP → ↑ protein kinase A → ↑ FBPase-2, ↓ PFK-2, less glycolysis, more gluconeogenesis.

Fed state: ↑ insulin → ↓ cAMP → ↓ protein kinase A → ↓ FBPase-2, ↑ PFK-2, more glycolysis, less gluconeogenesis.

Pyruvate dehydrogenase complex

Mitochondrial enzyme complex linking glycolysis and TCA cycle. Differentially regulated in fed/fasting states (active in fed state).

Reaction: pyruvate + NAD^+ + CoA → acetyl-CoA + CO_2 + NADH.

The complex contains 3 enzymes that require 5 cofactors:

1. **T**hiamine pyrophosphate (B_1)
2. **L**ipoic acid
3. **Co**A (B_5, pantothenic acid)
4. **F**AD (B_2, riboflavin)
5. **N**AD^+ (B_3, niacin)

Activated by:
↑ NAD^+/NADH ratio
↑ ADP
↑ Ca^{2+}

The complex is similar to the α-ketoglutarate dehydrogenase complex (same cofactors, similar substrate and action), which converts α-ketoglutarate → succinyl-CoA (TCA cycle).

The **L**ovely **Co**-enzymes **F**or **N**erds.

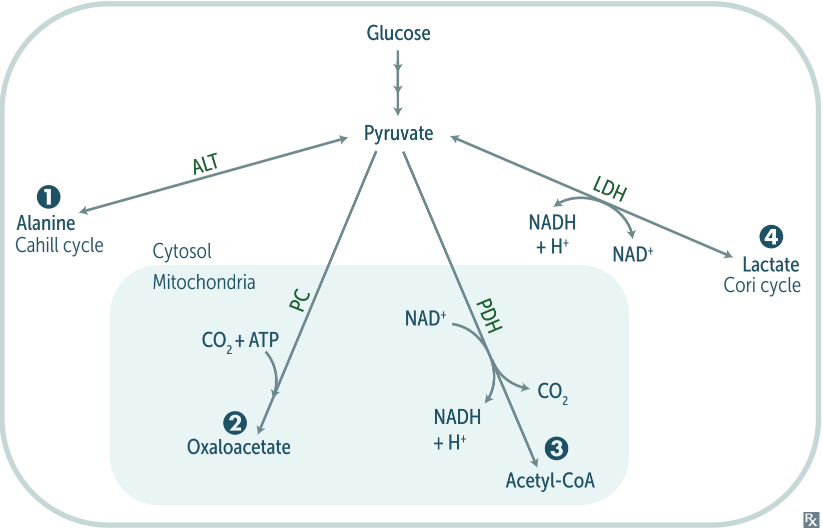
Arsenic inhibits lipoic acid. Arsenic poisoning clinical findings: vomiting, rice-water stools, garlic breath, QT prolongation.

Pyruvate dehydrogenase complex deficiency

Causes a buildup of pyruvate that gets shunted to lactate (via LDH) and alanine (via ALT). X-linked.

FINDINGS	Neurologic defects, lactic acidosis, ↑ serum alanine starting in infancy.	
TREATMENT	↑ intake of ketogenic nutrients (eg, high fat content or ↑ lysine and leucine).	Lysine and Leucine—the onLy pureLy ketogenic amino acids.

Pyruvate metabolism


Glucose
Pyruvate
ALT
❶
Alanine
Cahill cycle
Cytosol
Mitochondria
PC
CO_2 + ATP
❷
Oxaloacetate
PDH
NAD^+
CO_2
NADH
$+ H^+$
❸
Acetyl-CoA
LDH
NADH
$+ H^+$
NAD^+
❹
Lactate
Cori cycle

Functions of different pyruvate metabolic pathways (and their associated cofactors):

❶ Alanine aminotransferase (B_6): alanine carries amino groups to the liver from muscle

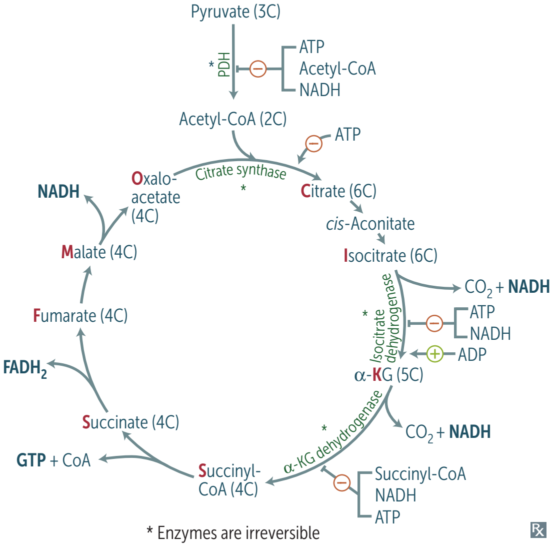
❷ Pyruvate carboxylase (biotin): oxaloacetate can replenish TCA cycle or be used in gluconeogenesis

❸ Pyruvate dehydrogenase (B_1, B_2, B_3, B_5, lipoic acid): transition from glycolysis to the TCA cycle

❹ Lactic acid dehydrogenase (B_3): end of anaerobic glycolysis (major pathway in RBCs, WBCs, kidney medulla, lens, testes, and cornea)

TCA cycle (Krebs cycle)

Pyruvate → acetyl-CoA produces 1 NADH, 1 CO_2.


Pyruvate (3C)
PDH
*
⊖
ATP
Acetyl-CoA
NADH
Acetyl-CoA (2C)
⊖ ATP
Citrate synthase
*
Oxalo-
acetate
(4C)
Citrate (6C)
cis-Aconitate
Isocitrate (6C)
CO_2 + NADH
Isocitrate dehydrogenase
*
⊖
ATP
NADH
⊕ ADP
α-KG (5C)
CO_2 + NADH
α-KG dehydrogenase
*
⊖
Succinyl-CoA
NADH
ATP
Succinyl-
CoA (4C)
GTP + CoA
Succinate (4C)
$FADH_2$
Fumarate (4C)
Malate (4C)
NADH

* Enzymes are irreversible

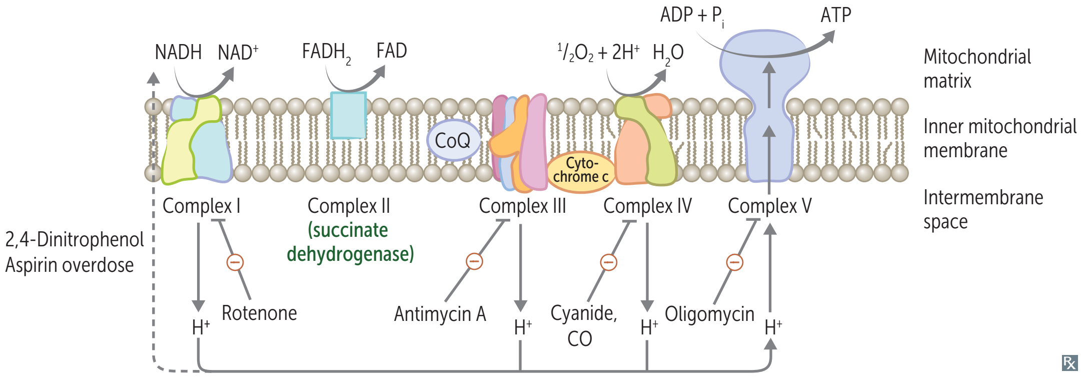
The TCA cycle produces 3 NADH, 1 $FADH_2$, 2 CO_2, 1 GTP per acetyl-CoA = 10 ATP/acetyl-CoA (2× everything per glucose). TCA cycle reactions occur in the mitochondria.

α-ketoglutarate dehydrogenase complex requires the same cofactors as the pyruvate dehydrogenase complex (B_1, B_2, B_3, B_5, lipoic acid).

Citrate Is Krebs' Starting Substrate For Making Oxaloacetate.

Electron transport chain and oxidative phosphorylation

NADH electrons from glycolysis enter mitochondria via the malate-aspartate or glycerol-3-phosphate shuttle. $FADH_2$ electrons are transferred to complex II (at a lower energy level than NADH). The passage of electrons results in the formation of a proton gradient that, coupled to oxidative phosphorylation, drives the production of ATP.


ADP + P_i
ATP
NADH
NAD^+
$FADH_2$
FAD
$^1/_2O_2 + 2H^+$
H_2O
Mitochondrial matrix
Inner mitochondrial membrane
Intermembrane space
CoQ
Cyto-chrome c
Complex I
Complex II (succinate dehydrogenase)
Complex III
Complex IV
Complex V
2,4-Dinitrophenol
Aspirin overdose
Rotenone
Antimycin A
Cyanide, CO
Oligomycin
H^+
H^+
H^+
H^+

ATP PRODUCED VIA ATP SYNTHASE

1 NADH → 2.5 ATP; 1 $FADH_2$ → 1.5 ATP.

OXIDATIVE PHOSPHORYLATION POISONS

Electron transport inhibitors	Directly inhibit electron transport, causing a ↓ proton gradient and block of ATP synthesis.	Rotenone: complex one inhibitor. "An-3-mycin" (antimycin) A: complex 3 inhibitor. CO/CN: complex 4 inhibitors (4 letters).
ATP synthase inhibitors	Directly inhibit mitochondrial ATP synthase, causing an ↑ proton gradient. No ATP is produced because electron transport stops.	Oligomycin.
Uncoupling agents	↑ permeability of membrane, causing a ↓ proton gradient and ↑ O_2 consumption. ATP synthesis stops, but electron transport continues. Produces heat.	2,4-Dinitrophenol (used illicitly for weight loss), aspirin (fevers often occur after aspirin overdose), thermogenin in brown fat.

Gluconeogenesis, irreversible enzymes		Pathway Produces Fresh Glucose.
Pyruvate carboxylase	In mitochondria. Pyruvate → oxaloacetate.	Requires biotin, ATP. Activated by acetyl-CoA.
Phosphoenolpyruvate carboxykinase	In cytosol. Oxaloacetate → phosphoenolpyruvate.	Requires GTP.
Fructose-1,6-bisphosphatase	In cytosol. Fructose-1,6-bisphosphate → fructose-6-phosphate.	Citrate ⊕, AMP ⊖, fructose 2,6-bisphosphate ⊖.
Glucose-6-phosphatase	In ER. Glucose-6-phosphate → glucose.	

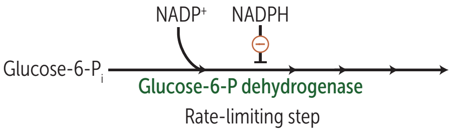
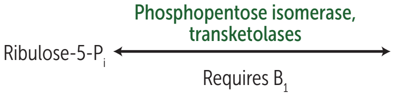
Occurs primarily in liver; serves to maintain euglycemia during fasting. Enzymes also found in kidney, intestinal epithelium. Deficiency of the key gluconeogenic enzymes causes hypoglycemia. (Muscle cannot participate in gluconeogenesis because it lacks glucose-6-phosphatase).

Odd-chain fatty acids yield 1 propionyl-CoA during metabolism, which can enter the TCA cycle (as succinyl-CoA), undergo gluconeogenesis, and serve as a glucose source. Even-chain fatty acids cannot produce new glucose, since they yield only acetyl-CoA equivalents.

HMP shunt (pentose phosphate pathway)

Provides a source of NADPH from abundantly available glucose-6-P (NADPH is required for reductive reactions, eg, glutathione reduction inside RBCs, fatty acid and cholesterol biosynthesis). Additionally, this pathway yields ribose for nucleotide synthesis and glycolytic intermediates. 2 distinct phases (oxidative and nonoxidative), both of which occur in the cytoplasm. No ATP is used or produced.

Sites: lactating mammary glands, liver, adrenal cortex (sites of fatty acid or steroid synthesis), RBCs.

REACTIONS	KEY ENZYMES	PRODUCTS
Oxidative (irreversible)	 NADP⁺ NADPH Glucose-6-Pᵢ Glucose-6-P dehydrogenase Rate-limiting step	CO_2 2 NADPH Ribulose-5-P_i
Nonoxidative (reversible)	 Phosphopentose isomerase, transketolases Ribulose-5-Pᵢ Requires B₁	Ribose-5-P_i Glyceraldehyde-3-phosphate Fructose-6-P

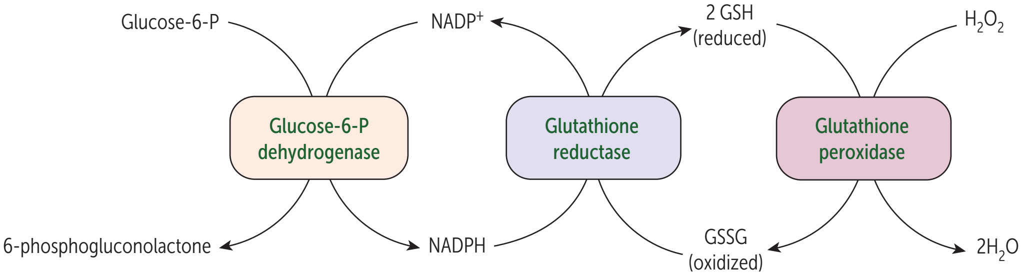
Glucose-6-phosphate dehydrogenase deficiency

NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. ↓ NADPH in RBCs leads to hemolytic anemia due to poor RBC defense against oxidizing agents (eg, fava beans, sulfonamides, primaquine, antituberculosis drugs). Infection (most common cause) can also precipitate hemolysis; inflammatory response produces free radicals that diffuse into RBCs, causing oxidative damage.

X-linked recessive disorder; most common human enzyme deficiency; more prevalent among African Americans. ↑ malarial resistance.

Heinz bodies—denatured **He**moglobin precipitates within RBCs due to oxidative stress.

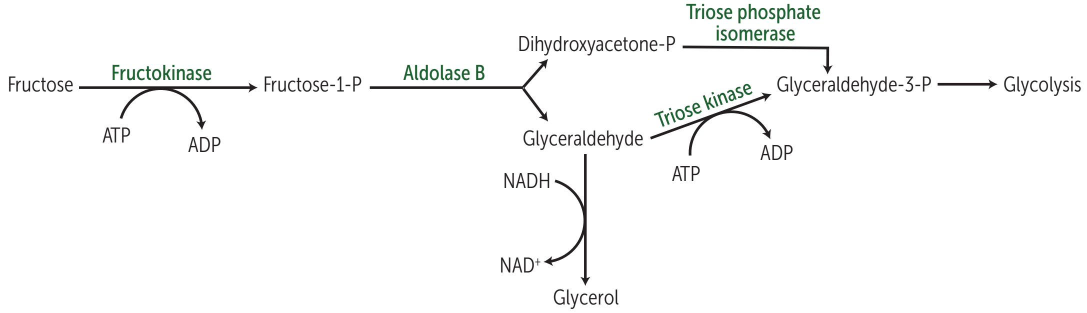
Bite cells—result from the phagocytic removal of **Heinz** bodies by splenic macrophages. Think, "**Bite** into some **Heinz** ketchup."


Glucose-6-P
NADP⁺
2 GSH (reduced)
H₂O₂
Glucose-6-P dehydrogenase
Glutathione reductase
Glutathione peroxidase
6-phosphogluconolactone
NADPH
GSSG (oxidized)
2H₂O

Disorders of fructose metabolism

Essential fructosuria	Involves a defect in **fructokinase**. Autosomal recessive. A benign, asymptomatic condition, since fructose is not trapped in cells. Symptoms: fructose appears in blood and urine. Disorders of fructose metabolism cause milder symptoms than analogous disorders of galactose metabolism.
Fructose intolerance	Hereditary deficiency of **aldolase B**. Autosomal recessive. Fructose-1-phosphate accumulates, causing a ↓ in available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis. Symptoms present following consumption of fruit, juice, or honey. Urine dipstick will be ⊖ (tests for glucose only); reducing sugar can be detected in the urine (nonspecific test for inborn errors of carbohydrate metabolism). Symptoms: hypoglycemia, jaundice, cirrhosis, vomiting. Treatment: ↓ intake of both fructose and sucrose (glucose + fructose).

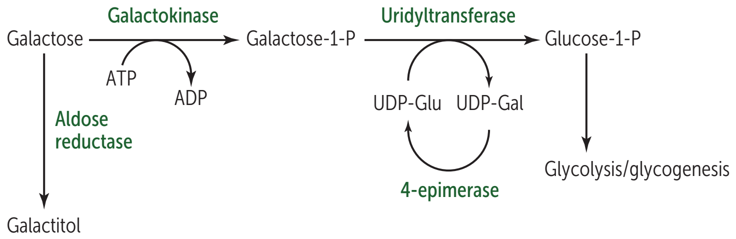
Fructose metabolism (liver)


Fructose
Fructokinase
ATP
ADP
Fructose-1-P
Aldolase B
Dihydroxyacetone-P
Triose phosphate isomerase
Glyceraldehyde-3-P
Glycolysis
Glyceraldehyde
Triose kinase
ATP
ADP
NADH
NAD+
Glycerol

Disorders of galactose metabolism

Galactokinase deficiency	Hereditary deficiency of **galactokinase**. Galactitol accumulates if galactose is present in diet. Relatively mild condition. Autosomal recessive. Symptoms: galactose appears in blood (galactosemia) and urine (galactosuria); infantile cataracts. May present as failure to track objects or to develop a social smile.
Classic galactosemia	Absence of **galactose-1-phosphate uridyltransferase**. Autosomal recessive. Damage is caused by accumulation of toxic substances (including galactitol, which accumulates in the lens of the eye). Symptoms develop when infant begins feeding (lactose present in breast milk and routine formula) and include failure to thrive, jaundice, hepatomegaly, infantile cataracts, intellectual disability. Can predispose to *E coli* sepsis in neonates. Treatment: exclude galactose and lactose (galactose + glucose) from diet.

Galactose metabolism


Galactose
Galactokinase
ATP
ADP
Galactose-1-P
Uridyltransferase
UDP-Glu
UDP-Gal
4-epimerase
Glucose-1-P
Glycolysis/glycogenesis
Aldose reductase
Galactitol

Fructose is to **A**ldolase **B** as **G**alactose is to **U**ridyl**T**ransferase (**FAB GUT**).

The more serious defects lead to PO_4^{3-} depletion.

Sorbitol

An alternative method of trapping glucose in the cell is to convert it to its alcohol counterpart, called sorbitol, via aldose reductase. Some tissues then convert sorbitol to fructose using sorbitol dehydrogenase; tissues with an insufficient amount/activity of this enzyme are at risk for intracellular sorbitol accumulation, causing osmotic damage (eg, cataracts, retinopathy, and peripheral neuropathy seen with chronic hyperglycemia in diabetes).

High blood levels of galactose also result in conversion to the osmotically active galactitol via aldose reductase.

Liver, ovaries, and seminal vesicles have both enzymes.

$$\text{Glucose} \xrightarrow[\text{NADPH}]{\text{Aldose reductase}} \text{Sorbitol} \xrightarrow[\text{NAD}^+]{\text{Sorbitol dehydrogenase}} \text{Fructose}$$

Lens has primarily aldose reductase. **R**etina, **K**idneys, and **S**chwann cells have only aldose reductase (**LuRKS**).

$$\text{Glucose} \xrightarrow[\text{NADPH}]{\text{Aldose reductase}} \text{Sorbitol}$$

Lactase deficiency

Insufficient lactase enzyme → dietary lactose intolerance. Lactase functions on the brush border to digest lactose (in human and cow milk) into glucose and galactose.

Primary: age-dependent decline after childhood (absence of lactase-persistent allele), common in people of Asian, African, or Native American descent.

Secondary: loss of brush border due to gastroenteritis (eg, rotavirus), autoimmune disease, etc.

Congenital lactase deficiency: rare, due to defective gene.

Stool demonstrates ↓ pH and breath shows ↑ hydrogen content with lactose hydrogen breath test. Intestinal biopsy reveals normal mucosa in patients with hereditary lactose intolerance.

FINDINGS	Bloating, cramps, flatulence, osmotic diarrhea.
TREATMENT	Avoid dairy products or add lactase pills to diet; lactose-free milk.

Amino acids

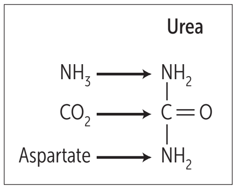
Only L-amino acids are found in proteins.

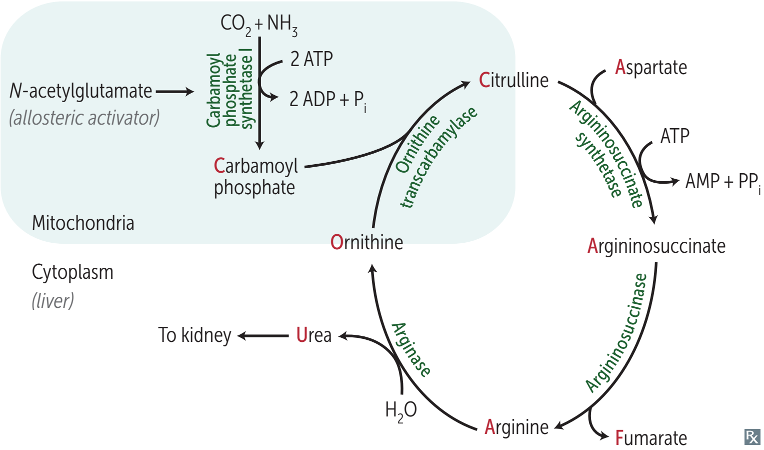
Essential	Glucogenic: methionine (**Met**), histidine (**His**), valine (**Val**). Glucogenic/ketogenic: isoleucine (Ile), phenylalanine (Phe), threonine (Thr), tryptophan (Trp). Ketogenic: leucine (Leu), lysine (Lys).	I **met his val**entine, she is so **sweet** (**gluco**genic). All essential amino acids need to be supplied in the diet.
Acidic	Aspartic acid (Asp) and glutamic acid (Glu). Negatively charged at body pH.	
Basic	Histidine (**His**), lysine (**Lys**), arginine (**Arg**). Arg is most **basic**. His has no charge at body pH.	**His lys** (lies) **are basic**. Arg and His are required during periods of growth. Arg and Lys are ↑ in histones, which bind negatively charged DNA.

Urea cycle

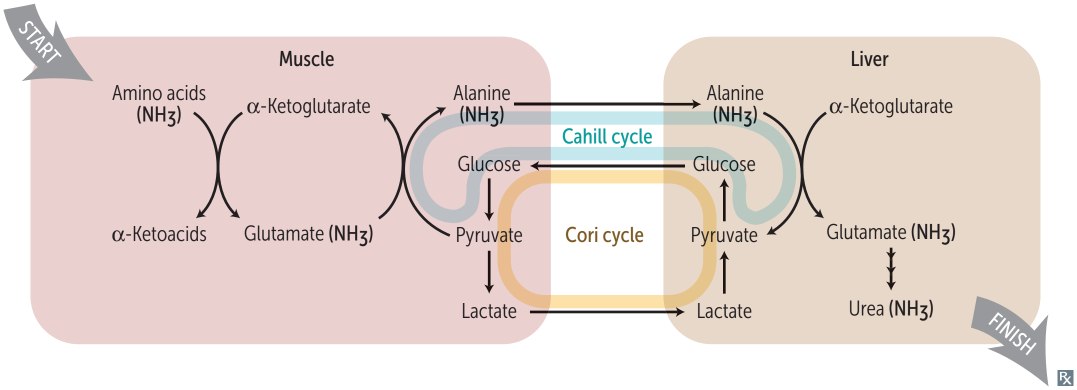
Amino acid catabolism results in the formation of common metabolites (eg, pyruvate, acetyl-CoA), which serve as metabolic fuels. Excess nitrogen generated by this process is converted to urea and excreted by the kidneys.

Ordinarily, **C**areless **C**rappers **A**re **A**lso **F**rivolous **A**bout **U**rination.

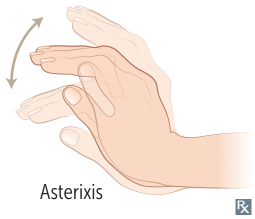

Urea
NH_3 → NH_2
CO_2 → C=O
Aspartate → NH_2


$CO_2 + NH_3$
2 ATP
2 ADP + P_i
Carbamoyl phosphate synthetase I
N-acetylglutamate
(allosteric activator)
Carbamoyl phosphate
Mitochondria
Ornithine transcarbamylase
Citrulline
Aspartate
Argininosuccinate synthetase
ATP
AMP + PP_i
Argininosuccinate
Argininosuccinase
Fumarate
Arginine
Arginase
H_2O
Urea
To kidney
Ornithine
Cytoplasm
(liver)

Transport of ammonia by alanine


START
Muscle
Amino acids (NH_3)
α-Ketoglutarate
α-Ketoacids
Glutamate (NH_3)
Alanine (NH_3)
Glucose
Pyruvate
Lactate
Cahill cycle
Cori cycle
Liver
Alanine (NH_3)
α-Ketoglutarate
Glucose
Pyruvate
Lactate
Glutamate (NH_3)
Urea (NH_3)
FINISH

Hyperammonemia


Asterixis

Can be acquired (eg, liver disease) or hereditary (eg, urea cycle enzyme deficiencies).

Results in excess NH_3, which depletes α-ketoglutarate, leading to inhibition of TCA cycle.

Treatment: limit protein in diet.

May be given to ↓ ammonia levels:

- Lactulose to acidify the GI tract and trap NH_4^+ for excretion.
- Antibiotics (eg, rifaximin) to ↓ colonic ammoniagenic bacteria.
- Benzoate, phenylacetate, or phenylbutyrate react with glycine or glutamine, forming products that are renally excreted.

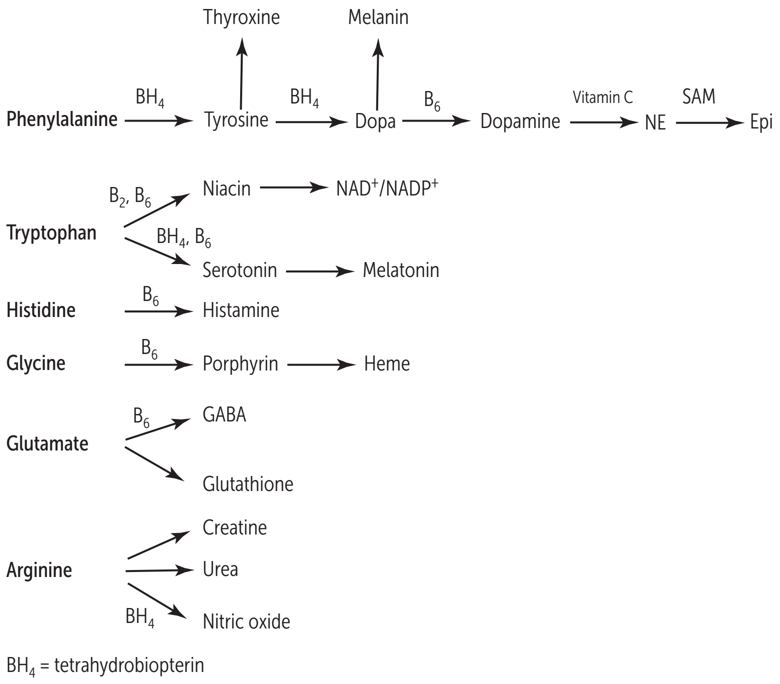
Ammonia accumulation—tremor (asterixis), slurring of speech, somnolence, vomiting, cerebral edema, blurring of vision.

Ornithine transcarbamylase deficiency

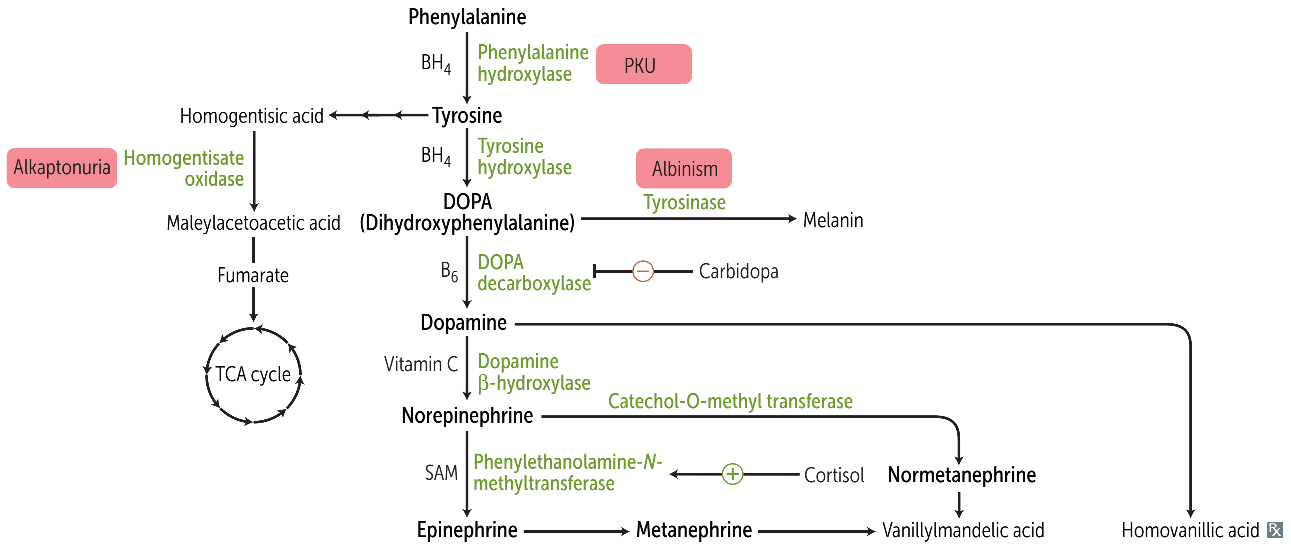
Most common urea cycle disorder. X-linked recessive (vs other urea cycle enzyme deficiencies, which are autosomal recessive). Interferes with the body's ability to eliminate ammonia. Often evident in the first few days of life, but may present later. Excess carbamoyl phosphate is converted to orotic acid (part of the pyrimidine synthesis pathway).

Findings: ↑ orotic acid in blood and urine, ↓ BUN, symptoms of hyperammonemia. No megaloblastic anemia (vs orotic aciduria).

Amino acid derivatives


Phenylalanine
BH4
Tyrosine
Thyroxine
BH4
Dopa
Melanin
B6
Dopamine
Vitamin C
NE
SAM
Epi
Tryptophan
B2, B6
Niacin
NAD+/NADP+
BH4, B6
Serotonin
Melatonin
Histidine
B6
Histamine
Glycine
B6
Porphyrin
Heme
Glutamate
B6
GABA
Glutathione
Arginine
Creatine
Urea
BH4
Nitric oxide
BH4 = tetrahydrobiopterin

Catecholamine synthesis/tyrosine catabolism


Phenylalanine
BH4
Phenylalanine hydroxylase
PKU
Tyrosine
Homogentisic acid
Alkaptonuria
Homogentisate oxidase
Maleylacetoacetic acid
Fumarate
TCA cycle
BH4
Tyrosine hydroxylase
Albinism
DOPA (Dihydroxyphenylalanine)
Tyrosinase
Melanin
B6
DOPA decarboxylase
Carbidopa
Dopamine
Vitamin C
Dopamine β-hydroxylase
Norepinephrine
Catechol-O-methyl transferase
SAM
Phenylethanolamine-N-methyltransferase
Cortisol
Normetanephrine
Epinephrine
Metanephrine
Vanillylmandelic acid
Homovanillic acid

Phenylketonuria

Due to ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin (BH_4) cofactor (malignant PKU). Tyrosine becomes essential. ↑ phenylalanine → excess phenyl ketones in urine.

Findings: intellectual disability, growth retardation, seizures, fair skin, eczema, musty body odor.

Treatment: ↓ phenylalanine and ↑ tyrosine in diet, tetrahydrobiopterin supplementation.

Maternal PKU—lack of proper dietary therapy during pregnancy. Findings in infant: microcephaly, intellectual disability, growth retardation, congenital heart defects.

Autosomal recessive. Incidence ≈ 1:10,000.

Screening occurs 2–3 days after birth (normal at birth because of maternal enzyme during fetal life).

Phenyl ketones—phenylacetate, phenyllactate, and phenylpyruvate.

Disorder of **aromatic** amino acid metabolism → musty body **odor.**

PKU patients must avoid the artificial sweetener aspartame, which contains phenylalanine.

Maple syrup urine disease

Blocked degradation of **branched** amino acids (**I**soleucine, **L**eucine, **V**aline) due to ↓ branched-chain α-ketoacid dehydrogenase (B_1). Causes ↑ α-ketoacids in the blood, especially those of leucine.

Causes severe CNS defects, intellectual disability, and death.

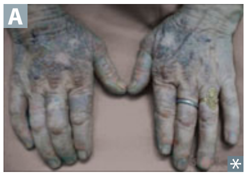
Treatment: restriction of isoleucine, leucine, valine in diet, and thiamine supplementation.

Autosomal recessive.

Presentation: vomiting, poor feeding, urine smells like maple syrup/burnt sugar.

I Love **V**ermont **maple syrup** from maple trees (with **B_1ranches**).

Alkaptonuria



Congenital deficiency of homogentisate oxidase in the degradative pathway of tyrosine to fumarate → pigment-forming homogentisic acid accumulates in tissue A. Autosomal recessive. Usually benign.

Findings: bluish-black connective tissue, ear cartilage, and sclerae (ochronosis); urine turns black on prolonged exposure to air. May have debilitating arthralgias (homogentisic acid toxic to cartilage).

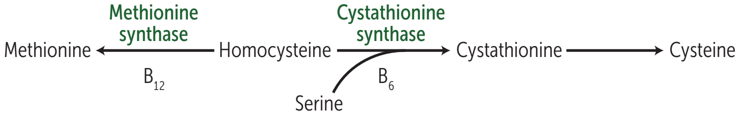
Homocystinuria

Types (all autosomal recessive):

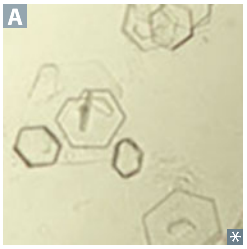
- Cystathionine synthase deficiency (treatment: ↓ methionine, ↑ cysteine, ↑ B_6, B_{12}, and folate in diet)
- ↓ affinity of cystathionine synthase for pyridoxal phosphate (treatment: ↑↑ B_6 and ↑ cysteine in diet)
- Methionine synthase (homocysteine methyltransferase) deficiency (treatment: ↑ methionine in diet)

All forms result in excess homocysteine.

HOMOCYstinuria: ↑↑ **H**omocysteine in urine, **O**steoporosis, **M**arfanoid habitus, **O**cular changes (downward and inward lens subluxation), **C**ardiovascular effects (thrombosis and atherosclerosis → stroke and MI), k**Y**phosis, intellectual disability.



Cystinuria



Hereditary defect of renal PCT and intestinal amino acid transporter that prevents reabsorption of **C**ystine, **O**rnithine, **L**ysine, and **A**rginine (**COLA**).

Excess cystine in the urine can lead to recurrent precipitation of hexagonal cystine stones A.

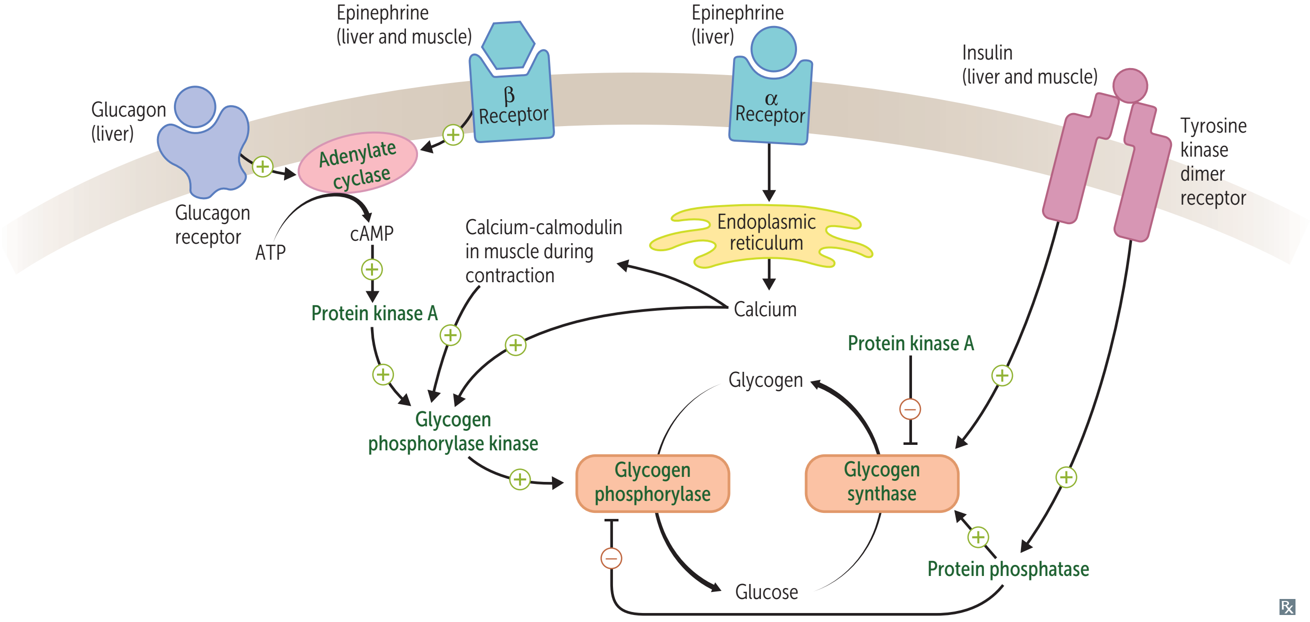
Treatment: urinary alkalinization (eg, potassium citrate, acetazolamide) and chelating agents (eg, penicillamine) ↑ solubility of cystine stones; good hydration.

Autosomal recessive. Common (1:7000).

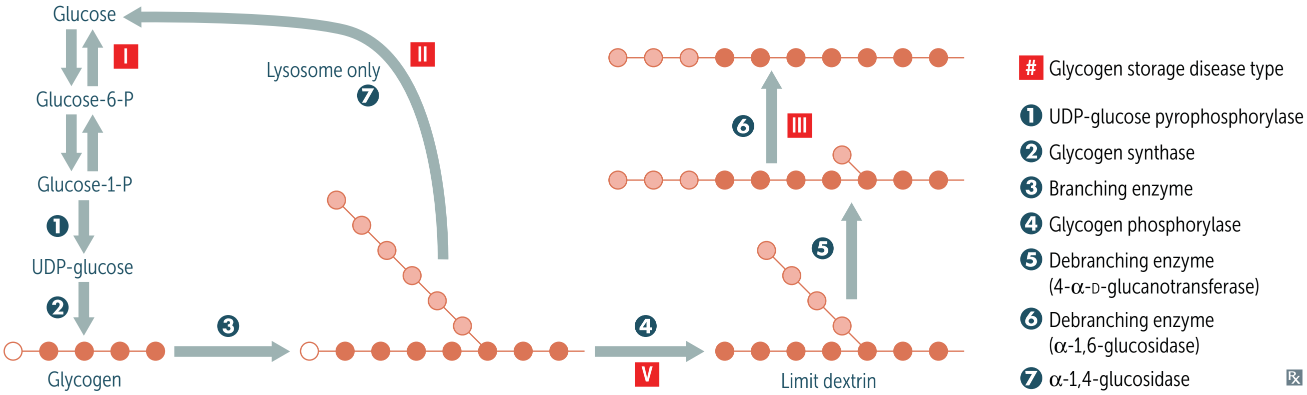
Urinary cyanide-nitroprusside test is diagnostic.

Cystine is made of 2 cysteines connected by a disulfide bond.

Glycogen regulation by insulin and glucagon/epinephrine


Epinephrine (liver and muscle)
Epinephrine (liver)
Insulin (liver and muscle)
Glucagon (liver)
β Receptor
α Receptor
Tyrosine kinase dimer receptor
Adenylate cyclase
Glucagon receptor
ATP
cAMP
Calcium-calmodulin in muscle during contraction
Endoplasmic reticulum
Calcium
Protein kinase A
Protein kinase A
Glycogen
Glycogen phosphorylase kinase
Glycogen phosphorylase
Glycogen synthase
Protein phosphatase
Glucose
+
−

Glycogen	Branches have α-(1,6) bonds; linkages have α-(1,4) bonds.
Skeletal muscle	Glycogen undergoes glycogenolysis → glucose-1-phosphate → glucose-6-phosphate, which is rapidly metabolized during exercise.
Hepatocytes	Glycogen is stored and undergoes glycogenolysis to maintain blood sugar at appropriate levels. Glycogen phosphorylase ❹ liberates glucose-1-phosphate residues off branched glycogen until 4 glucose units remain on a branch. Then 4-α-D-glucanotransferase (debranching enzyme ❺) moves 3 molecules of glucose-1-phosphate from the branch to the linkage. Then α-1,6-glucosidase (debranching enzyme ❻) cleaves off the last residue, liberating glucose. "Limit dextrin" refers to the one to four residues remaining on a branch after glycogen phosphorylase has already shortened it.


Glucose
I
Glucose-6-P
Glucose-1-P
❶
UDP-glucose
❷
Glycogen
❸
Lysosome only
❼
II
❹
V
Limit dextrin
❺
❻
III
# Glycogen storage disease type
❶ UDP-glucose pyrophosphorylase
❷ Glycogen synthase
❸ Branching enzyme
❹ Glycogen phosphorylase
❺ Debranching enzyme (4-α-D-glucanotransferase)
❻ Debranching enzyme (α-1,6-glucosidase)
❼ α-1,4-glucosidase

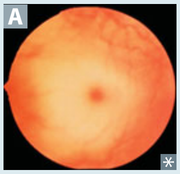
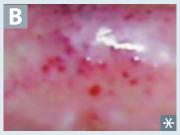
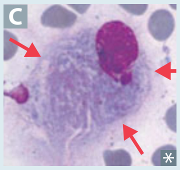
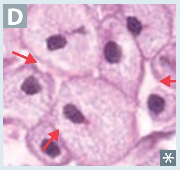
Note: A small amount of glycogen is degraded in lysosomes by ❼ α-1,4-glucosidase (acid maltase).

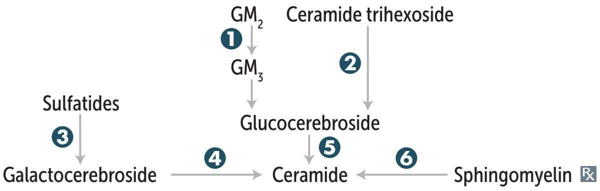
Glycogen storage diseases	12 types, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells. Periodic acid–Schiff stain identifies glycogen and is useful in identifying these diseases.	Very Poor Carbohydrate Metabolism. Types I, II, III, and V are autosomal recessive.

DISEASE	FINDINGS	DEFICIENT ENZYME	COMMENTS
Von Gierke disease (type I)	Severe fasting hypoglycemia, ↑↑ Glycogen in liver, ↑ blood lactate, ↑ triglycerides, ↑ uric acid (Gout), and hepatomegaly.	Glucose-6-phosphatase	Treatment: frequent oral glucose/cornstarch; avoidance of fructose and galactose Impaired gluconeogenesis and glycogenolysis
Pompe disease (type II)	Cardiomegaly, hypertrophic cardiomyopathy, hypotonia, exercise intolerance, and systemic findings lead to early death.	Lysosomal acid α-1,4-glucosidase with α-1,6-glucosidase activity (acid maltase)	PomPe trashes the PumP (1,4) (heart, liver, and muscle)
Cori disease (type III)	Milder form of von Gierke (type I) with normal blood lactate levels. Accumulation of limit dextrin–like structures in cytosol.	Debranching enzyme (α-1,6-glucosidase)	Gluconeogenesis is intact
McArdle disease (type V)	↑ glycogen in muscle, but muscle cannot break it down → painful Muscle cramps, Myoglobinuria (red urine) with strenuous exercise, and arrhythmia from electrolyte abnormalities. Second-wind phenomenon noted during exercise due to ↑ muscular blood flow.	Skeletal muscle glycogen phosphorylase (Myophosphorylase)	Blood glucose levels typically unaffected McArdle = Muscle

Lysosomal storage diseases

Each is caused by a deficiency in one of the many lysosomal enzymes. Results in an accumulation of abnormal metabolic products.

DISEASE	FINDINGS	DEFICIENT ENZYME	ACCUMULATED SUBSTRATE	INHERITANCE
Sphingolipidoses				
Tay-Sachs disease 	Progressive neurodegeneration, developmental delay, "cherry-red" spot on macula A, lysosomes with onion skin, no hepatosplenomegaly (vs Niemann-Pick).	❶ He**X**osaminidase **A** ("T**A**y-Sa**X**")	GM_2 ganglioside	AR
Fabry disease 	Early: Triad of episodic peripheral neuropathy, angiokeratomas B, hypohidrosis. Late: progressive renal failure, cardiovascular disease.	❷ α-galactosidase A	Ceramide trihexoside	XR
Metachromatic leukodystrophy	Central and peripheral demyelination with ataxia, dementia.	❸ Arylsulfatase A	Cerebroside sulfate	AR
Krabbe disease	Peripheral neuropathy, destruction of oligodendrocytes, developmental delay, optic atrophy, globoid cells.	❹ Galactocerebrosidase	Galactocerebroside, psychosine	AR
Gaucher disease 	Most common. Hepatosplenomegaly, pancytopenia, osteoporosis, avascular necrosis of femur, bone crises, Gaucher cells C (lipid-laden macrophages resembling crumpled tissue paper).	❺ Glucocerebrosidase (β-glucosidase); treat with recombinant glucocerebrosidase	Glucocerebroside	AR
Niemann-Pick disease 	Progressive neurodegeneration, hepatosplenomegaly, foam cells (lipid-laden macrophages) D, "cherry-red" spot on macula A.	❻ Sphingomyelinase	Sphingomyelin	AR
Mucopolysaccharidoses				
Hurler syndrome	Developmental delay, gargoylism, airway obstruction, corneal clouding, hepatosplenomegaly.	α-L-iduronidase	Heparan sulfate, dermatan sulfate	AR
Hunter syndrome	Mild Hurler + aggressive behavior, no corneal clouding.	Iduronate sulfatase	Heparan sulfate, dermatan sulfate	XR



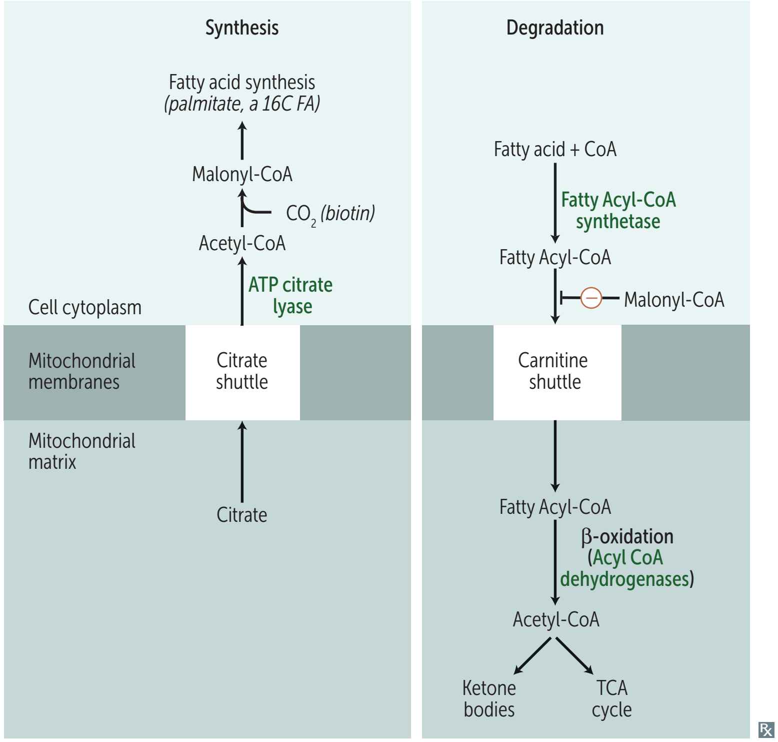
No man picks (**Niemann-Pick**) his nose with his **sphing**er (**sphing**omyelinase).

Tay-Sa**X** lacks he**X**osaminidase.

Hunters see clearly (no corneal clouding) and aggressively aim for the **X** (**X**-linked recessive).

↑ incidence of Tay-Sachs, Niemann-Pick, and some forms of Gaucher disease in Ashkenazi Jews.

Fatty acid metabolism


Synthesis
Fatty acid synthesis
(palmitate, a 16C FA)
Malonyl-CoA
CO₂ (biotin)
Acetyl-CoA
ATP citrate lyase
Cell cytoplasm
Mitochondrial membranes
Citrate shuttle
Mitochondrial matrix
Citrate
Degradation
Fatty acid + CoA
Fatty Acyl-CoA synthetase
Fatty Acyl-CoA
Malonyl-CoA
Carnitine shuttle
Fatty Acyl-CoA
β-oxidation
(Acyl CoA dehydrogenases)
Acetyl-CoA
Ketone bodies
TCA cycle

Fatty acid synthesis requires transport of citrate from mitochondria to cytosol. Predominantly occurs in liver, lactating mammary glands, and adipose tissue.

Long-chain fatty acid (LCFA) degradation requires carnitine-dependent transport into the mitochondrial matrix.

"**SY**trate" = **SY**nthesis.

CARnitine = **CAR**nage of fatty acids.

Systemic 1° carnitine deficiency—inherited defect in transport of LCFAs into the mitochondria → toxic accumulation. Causes weakness, hypotonia, and hypoketotic hypoglycemia.

Medium-chain acyl-CoA dehydrogenase deficiency—↓ ability to break down fatty acids into acetyl-CoA → accumulation of fatty acyl carnitines in the blood with hypoketotic hypoglycemia. Causes vomiting, lethargy, seizures, coma, liver dysfunction. Can lead to sudden death in infants or children. Treat by avoiding fasting.

Ketone bodies

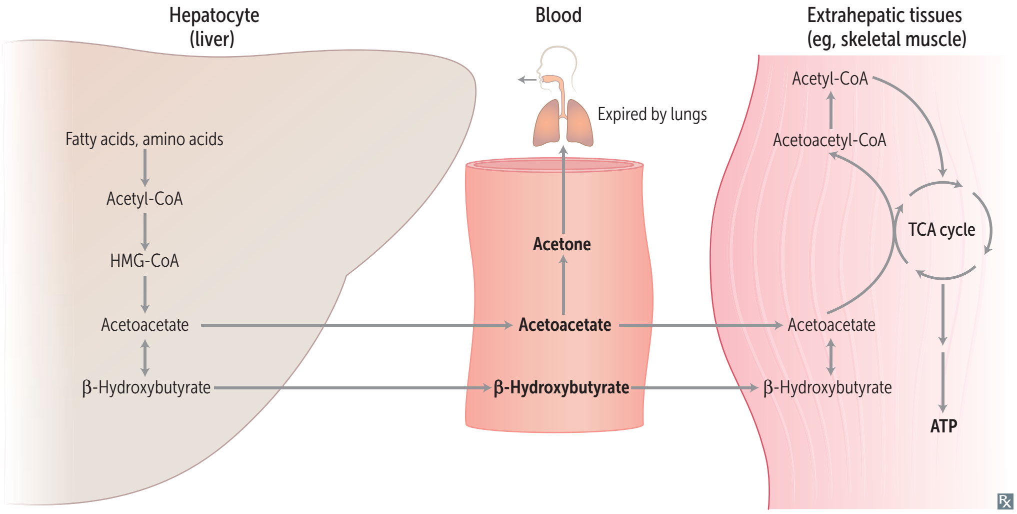
In the liver, fatty acids and amino acids are metabolized to acetoacetate and β-hydroxybutyrate (to be used in muscle and brain).

In prolonged starvation and diabetic ketoacidosis, oxaloacetate is depleted for gluconeogenesis. In alcoholism, excess NADH shunts oxaloacetate to malate. Both processes cause a buildup of acetyl-CoA, which shunts glucose and FFA toward the production of ketone bodies.

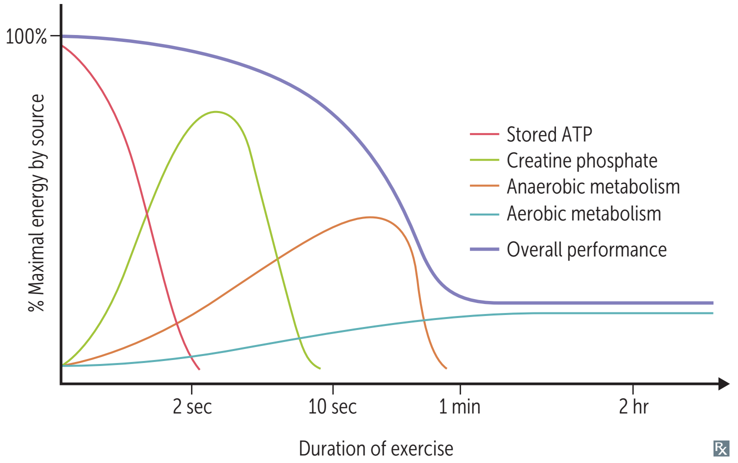
Ketone bodies: acetone, acetoacetate, β-hydroxybutyrate.

Breath smells like acetone (fruity odor).

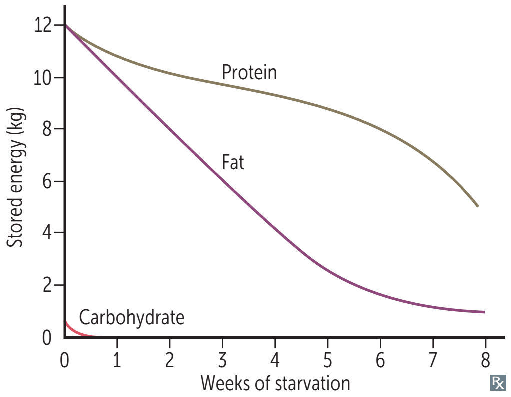
Urine test for ketones can detect acetoacetate, but not β-hydroxybutyrate.


Hepatocyte (liver)
Blood
Extrahepatic tissues (eg, skeletal muscle)
Fatty acids, amino acids
Acetyl-CoA
HMG-CoA
Acetoacetate
β-Hydroxybutyrate
Expired by lungs
Acetone
Acetoacetate
β-Hydroxybutyrate
Acetyl-CoA
Acetoacetyl-CoA
TCA cycle
Acetoacetate
β-Hydroxybutyrate
ATP

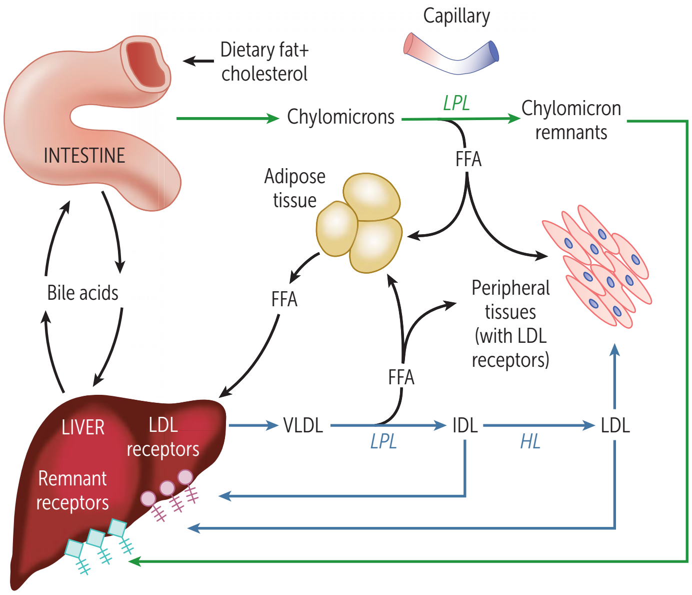
Metabolic fuel use



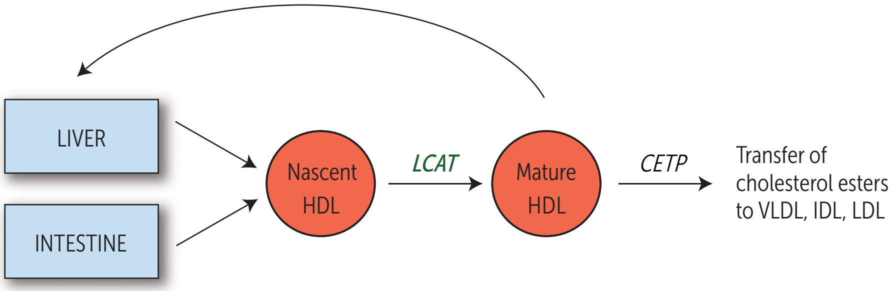
kcal (# letters = # kcal)
1g **carb** = **4** kcal
1g **alcohol** = **7** kcal
1g **fatty acid** = **9** kcal

Fasting and starvation	Priorities are to supply sufficient glucose to the brain and RBCs and to preserve protein.	
Fed state (after a meal)	Glycolysis and aerobic respiration.	Insulin stimulates storage of lipids, proteins, and glycogen.
Fasting (between meals)	Hepatic glycogenolysis (major); hepatic gluconeogenesis, adipose release of FFA (minor).	Glucagon and epinephrine stimulate use of fuel reserves.
Starvation days 1–3	Blood glucose levels maintained by: ▪ Hepatic glycogenolysis ▪ Adipose release of FFA ▪ Muscle and liver, which shift fuel use from glucose to FFA ▪ Hepatic gluconeogenesis from peripheral tissue lactate and alanine, and from adipose tissue glycerol and propionyl-CoA (from odd-chain FFA—the only triacylglycerol components that contribute to gluconeogenesis)	Glycogen reserves depleted after day 1. RBCs lack mitochondria and therefore cannot use ketones. 
Starvation after day 3	Adipose stores (ketone bodies become the main source of energy for the brain). After these are depleted, vital protein degradation accelerates, leading to organ failure and death. Amount of excess stores determines survival time.	

Lipid transport, key enzymes


Capillary
Dietary fat+ cholesterol
INTESTINE
Chylomicrons
LPL
Chylomicron remnants
FFA
Adipose tissue
Bile acids
FFA
Peripheral tissues (with LDL receptors)
FFA
LIVER
LDL receptors
Remnant receptors
VLDL
LPL
IDL
HL
LDL

Pancreatic lipase—degradation of dietary triglycerides (TGs) in small intestine.
Lipoprotein lipase (LPL)—degradation of TGs circulating in chylomicrons and VLDLs. Found on vascular endothelial surface.
Hepatic TG lipase (HL)—degradation of TGs remaining in IDL.
Hormone-sensitive lipase—degradation of TGs stored in adipocytes.


LIVER
INTESTINE
Nascent HDL
LCAT
Mature HDL
CETP
Transfer of cholesterol esters to VLDL, IDL, LDL

LCAT—catalyzes esterification of ⅔ of plasma cholesterol.
Cholesterol ester transfer protein (CETP)—mediates transfer of cholesterol esters to other lipoprotein particles.

Major apolipoproteins

Apolipoprotein	Function	Chylomicron	Chylomicron remnant	VLDL	IDL	LDL	HDL
E	Mediates remnant uptake (**E**verything **E**xcept LDL)	✓	✓	✓	✓		✓
A-I	**A**ctivates LCAT	✓					✓
C-II	Lipoprotein lipase **C**ofactor that **C**atalyzes **C**leavage	✓		✓			✓
B-48	Mediates chylomicron secretion into lymphatics	✓	✓				
B-100	Binds LDL receptor			✓	✓	✓	

Lipoprotein functions	Lipoproteins are composed of varying proportions of cholesterol, TGs, and phospholipids. LDL and HDL carry the most cholesterol. LDL transports cholesterol from liver to tissues. HDL transports cholesterol from periphery to liver.	 **L**DL is **L**ousy. **H**DL is **H**ealthy.
Cholesterol	Needed to maintain cell membrane integrity and synthesize bile acid, steroids, and vitamin D.	
Chylomicron	Delivers dietary TGs to peripheral tissues. Delivers cholesterol to liver in the form of chylomicron remnants, which are mostly depleted of their TGs. Secreted by intestinal epithelial cells.	
VLDL	Delivers hepatic TGs to peripheral tissue. Secreted by liver.	
IDL	Formed in the degradation of VLDL. Delivers TGs and cholesterol to liver.	
LDL	Delivers hepatic cholesterol to peripheral tissues. Formed by hepatic lipase modification of IDL in the liver and peripheral tissue. Taken up by target cells via receptor-mediated endocytosis.	
HDL	Mediates reverse cholesterol transport from periphery to liver. Acts as a repository for apolipoproteins C and E (which are needed for chylomicron and VLDL metabolism). Secreted from both liver and intestine. Alcohol ↑ synthesis.	

Abetalipoproteinemia	Autosomal recessive. Chylomicrons, VLDL, LDL absent. Deficiency in ApoB48, ApoB100. Affected infants present with severe fat malabsorption, steatorrhea, failure to thrive. Later manifestations include retinitis pigmentosa, spinocerebellar degeneration due to vitamin E deficiency, progressive ataxia, acanthocytosis. Treatment: restriction of long-chain fatty acids, large doses of oral vitamin E.

Familial dyslipidemias

TYPE	INHERITANCE	PATHOGENESIS	↑ BLOOD LEVEL	CLINICAL
I—Hyper-chylomicronemia	AR	Lipoprotein lipase or apolipoprotein C-II deficiency	Chylomicrons, TG, cholesterol	Pancreatitis, hepatosplenomegaly, and eruptive/pruritic xanthomas (no ↑ risk for atherosclerosis). Creamy layer in supernatant.
II—Familial hyper-cholesterolemia	AD	Absent or defective LDL receptors	IIa: LDL, cholesterol IIb: LDL, cholesterol, VLDL	Heterozygotes (1:500) have cholesterol ≈ 300mg/dL; homozygotes (very rare) have cholesterol ≈ 700+ mg/dL. Accelerated atherosclerosis (may have MI before age 20), tendon (Achilles) xanthomas, and corneal arcus.
III—Dysbeta-lipoproteinemia	AR	Defective ApoE	Chylomicrons, VLDL	Premature atherosclerosis, tuberoeruptive xanthomas, xanthoma striatum palmare.
IV—Hyper-triglyceridemia	AD	Hepatic overproduction of VLDL	VLDL, TG	Hypertriglyceridemia (> 1000 mg/dL) can cause acute pancreatitis.

HIGH-YIELD PRINCIPLES IN

Immunology

"I hate to disappoint you, but my rubber lips are immune to your charms."
—*Batman & Robin*

"No State shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States . . ."
—The United States Constitution

Mastery of the basic principles and facts in the immunology section will be useful for the Step 1 exam. Cell surface markers are important to know because they are clinically useful (eg, in identifying specific types of immunodeficiency or cancer) and are functionally critical to the jobs immune cells carry out. By spending a little extra effort here, it is possible to turn a traditionally difficult subject into one that is high yield.

▸ Lymphoid Structures 92
▸ Lymphocytes 95
▸ Immune Responses 102
▸ Immunosuppressants 116

▶ IMMUNOLOGY—LYMPHOID STRUCTURES

Immune system organs

1° organs:
- Bone marrow—immune cell production, B cell maturation
- Thymus—T cell maturation

2° organs:
- Spleen, lymph nodes, tonsils, Peyer patches
- Allow immune cells to interact with antigen

Lymph node

A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae. Functions are nonspecific filtration by macrophages, storage of B and T cells, and immune response activation.

Follicle

Site of B-cell localization and proliferation. In outer cortex. 1° follicles are dense and dormant. 2° follicles have pale central germinal centers and are active.

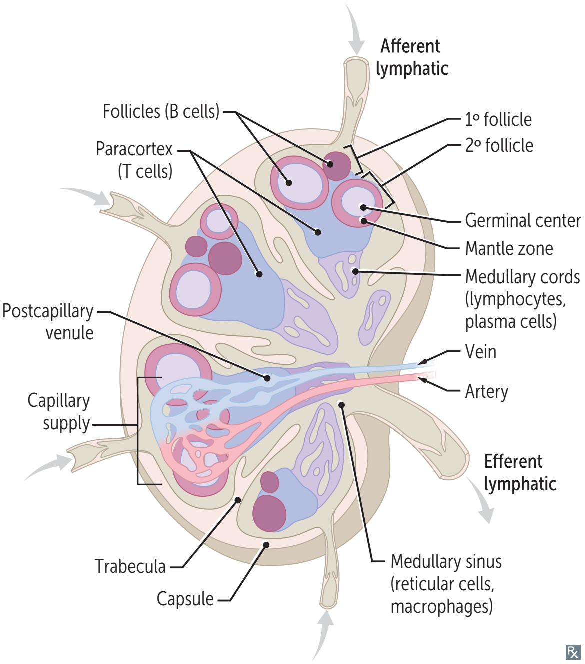
Medulla

Consists of medullary cords (closely packed lymphocytes and plasma cells) and medullary sinuses. Medullary sinuses communicate with efferent lymphatics and contain reticular cells and macrophages.

Paracortex

Houses T cells. Region of cortex between follicles and medulla. Contains high endothelial venules through which T and B cells enter from blood. Not well developed in patients with DiGeorge syndrome.

Paracortex enlarges in an extreme cellular immune response (eg, viral infection).

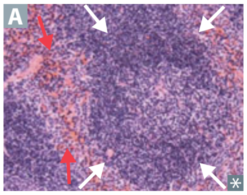

Afferent lymphatic
Follicles (B cells)
Paracortex (T cells)
1° follicle
2° follicle
Germinal center
Mantle zone
Medullary cords (lymphocytes, plasma cells)
Postcapillary venule
Vein
Artery
Capillary supply
Efferent lymphatic
Trabecula
Capsule
Medullary sinus (reticular cells, macrophages)

Lymph drainage

LYMPH NODE CLUSTER	AREA OF BODY DRAINED
Cervical	Head and neck
Hilar	Lungs
Mediastinal	Trachea and esophagus
Axillary	Upper limb, breast, skin above umbilicus
Celiac	Liver, stomach, spleen, pancreas, upper duodenum
Superior mesenteric	Lower duodenum, jejunum, ileum, colon to splenic flexure
Inferior mesenteric	Colon from splenic flexure to upper rectum
Internal iliac	Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), cervix, prostate
Para-aortic	Testes, ovaries, kidneys, uterus
Superficial inguinal	Anal canal (below pectinate line), skin below umbilicus (except popliteal area), scrotum, vulva
Popliteal	Dorsolateral foot, posterior calf

Right lymphatic duct drains right side of body above diaphragm.
Thoracic duct drains everything else into junction of left subclavian and internal jugular veins.

Spleen



Located in LUQ of abdomen, anterior to left kidney, protected by 9th-11th ribs.

Sinusoids are long, vascular channels in red pulp (red arrows in A) with fenestrated "barrel hoop" basement membrane.

- T cells are found in the periarteriolar lymphatic sheath (PALS) within the white pulp (white arrows in A).
- B cells are found in follicles within the white pulp.
- The marginal zone, in between the red pulp and white pulp, contains macrophages and specialized B cells, and is where antigen-presenting cells (APCs) capture blood-borne antigens for recognition by lymphocytes.

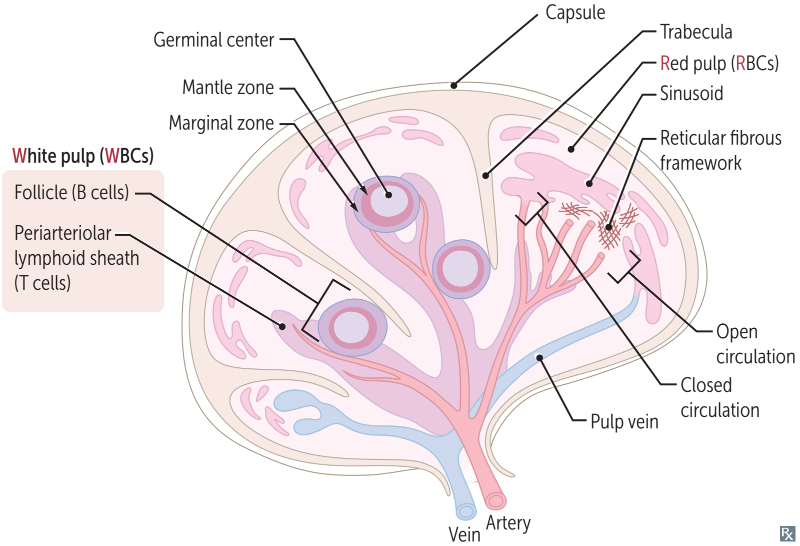
Macrophages found nearby in spleen remove encapsulated bacteria.

Splenic dysfunction (eg, postsplenectomy, sickle cell disease): ↓ IgM → ↓ complement activation → ↓ C3b opsonization → ↑ susceptibility to encapsulated organisms.

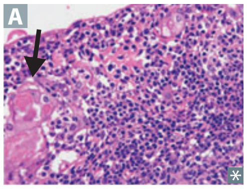
Postsplenectomy:

- Howell-Jolly bodies (nuclear remnants)
- Target cells
- Thrombocytosis (loss of sequestration and removal)
- Lymphocytosis (loss of sequestration)

Vaccinate patients undergoing splenectomy against encapsulated organisms (pneumococcal, Hib, meningococcal).


Capsule
Germinal center
Trabecula
Red pulp (RBCs)
Mantle zone
Sinusoid
Marginal zone
Reticular fibrous framework
White pulp (WBCs)
Follicle (B cells)
Periarteriolar lymphoid sheath (T cells)
Open circulation
Closed circulation
Pulp vein
Vein
Artery

Thymus



Located in the anterosuperior mediastinum. Site of T-cell differentiation and maturation. Encapsulated. Thymus is derived from the Third pharyngeal pouch. Lymphocytes of mesenchymal origin. Cortex is dense with immature T cells; medulla is pale with mature T cells and Hassall corpuscles A containing epithelial reticular cells.

T cells = Thymus

B cells = Bone marrow

Hypoplastic in DiGeorge syndrome and severe combined immunodeficiency (SCID).

Thymoma—benign neoplasm of thymus. Associated with myasthenia gravis and superior vena cava syndrome.

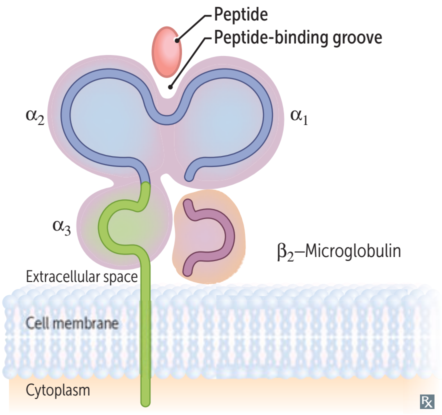
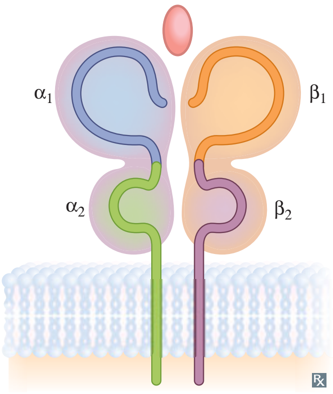
▶ IMMUNOLOGY—LYMPHOCYTES

Innate vs adaptive immunity

	Innate immunity	Adaptive immunity
COMPONENTS	Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement	T cells, B cells, circulating antibodies
MECHANISM	Germline encoded	Variation through V(D)J recombination during lymphocyte development
RESISTANCE	Resistance persists through generations; does not change within an organism's lifetime	Microbial resistance not heritable
RESPONSE TO PATHOGENS	Nonspecific Occurs rapidly (minutes to hours) No memory response	Highly specific, refined over time Develops over long periods; memory response is faster and more robust
PHYSICAL BARRIERS	Epithelial tight junctions, mucus	—
SECRETED PROTEINS	Lysozyme, complement, C-reactive protein (CRP), defensins	Immunoglobulins
KEY FEATURES IN PATHOGEN RECOGNITION	Toll-like receptors (TLRs): pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs). Examples of PAMPs include LPS (gram ⊖ bacteria), flagellin (bacteria), nucleic acids (viruses).	Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen → stronger, quicker immune response

Major histocompatibility complex I and II

MHC encoded by HLA genes. Present antigen fragments to T cells and bind T-cell receptors (TCRs).

	MHC I	MHC II
LOCI	HLA-A, HLA-B, HLA-C MHC I loci have 1 letter	HLA-DP, HLA-DQ, HLA-DR MHC II loci have 2 letters
BINDING	TCR and CD8	TCR and CD4
STRUCTURE	1 long chain, 1 short chain	2 equal-length chains
EXPRESSION	All nucleated cells, APCs, platelets Not on RBCs	APCs
FUNCTION	Present **endogenously** synthesized **antigens** (eg, viral or cytosolic proteins) to **CD8+ cytotoxic T cells**	Present **exogenously** synthesized **antigens** (eg, bacterial proteins) to **CD4+ helper T cells**
ANTIGEN LOADING	Antigen peptides loaded onto MHC I in RER after delivery via TAP (transporter associated with antigen processing)	Antigen loaded following release of invariant chain in an acidified endosome
ASSOCIATED PROTEINS	β_2-microglobulin	Invariant chain
STRUCTURE	 Peptide Peptide-binding groove α_2 α_1 α_3 β_2–Microglobulin Extracellular space Cell membrane Cytoplasm	

HLA subtypes associated with diseases

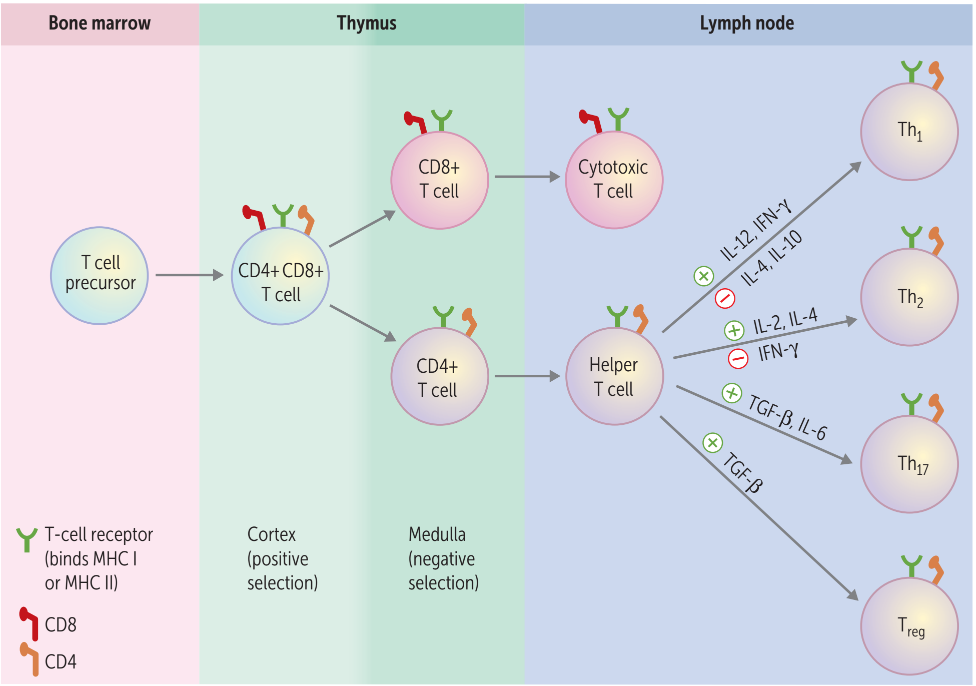
A3	Hemochromatosis	
B8	Addison disease, myasthenia gravis, Graves disease	
B27	Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis	PAIR. Also known as seronegative arthropathies.
DQ2/DQ8	Celiac disease	I ate (8) too (2) much gluten at Dairy Queen.
DR2	Multiple sclerosis, hay fever, SLE, Goodpasture syndrome	Multiple hay pastures have dirt.
DR3	Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease	2-3, S-L-E
DR4	Rheumatoid arthritis, diabetes mellitus type 1, Addison disease	There are 4 walls in a “rheum” (room).
DR5	Pernicious anemia → vitamin B_{12} deficiency, Hashimoto thyroiditis	

Natural killer cells	Lymphocyte member of innate immune system. Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells. Activity enhanced by IL-2, IL-12, IFN-α, and IFN-β. Induced to kill when exposed to a nonspecific activation signal on target cell and/or to an absence of MHC I on target cell surface. Also kills via antibody-dependent cell-mediated cytotoxicity (CD16 binds Fc region of bound Ig, activating the NK cell).

Major functions of B and T cells

B cells	Humoral immunity. Recognize antigen—undergo somatic hypermutation to optimize antigen specificity. Produce antibody—differentiate into plasma cells to secrete specific immunoglobulins. Maintain immunologic memory—memory B cells persist and accelerate future response to antigen.
T cells	Cell-mediated immunity. CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes. CD8+ T cells directly kill virus-infected cells. Delayed cell-mediated hypersensitivity (type IV). Acute and chronic cellular organ rejection. **Rule of 8**: MHC **II** × CD**4** = **8**; MHC **I** × CD**8** = **8**.

Differentiation of T cells


Bone marrow
Thymus
Lymph node
T cell precursor
CD4+CD8+ T cell
CD8+ T cell
CD4+ T cell
Cytotoxic T cell
Helper T cell
⊕ IL-12, IFN-γ
⊖ IL-4, IL-10
⊕ IL-2, IL-4
⊖ IFN-γ
⊕ TGF-β, IL-6
⊕ TGF-β
Th1
Th2
Th17
Treg
T-cell receptor (binds MHC I or MHC II)
CD8
CD4
Cortex (positive selection)
Medulla (negative selection)

Positive selection	Thymic cortex. T cells expressing TCRs capable of binding self-MHC on cortical epithelial cells survive.
Negative selection	Thymic medulla. T cells expressing TCRs with high affinity for self antigens undergo apoptosis. Tissue-restricted self-antigens are expressed in the thymus due to the action of autoimmune regulator (AIRE); deficiency leads to autoimmune polyendocrine syndrome-1.

Helper T cells

Th1 cell	Th2 cell
Secretes IFN-γ and IL-2	Secretes IL-4, IL-5, IL-6, IL-10, IL-13
Activates macrophages and cytotoxic T cells	Recruits eosinophils for parasite defense and promotes IgE production by B cells
Differentiation induced by IFN-γ and IL-12	Differentiation induced by IL-2 and IL-4
Inhibited by IL-4 and IL-10 (from Th2 cell)	Inhibited by IFN-γ (from Th1 cell)

Macrophage-lymphocyte interaction—dendritic cells, macrophages, and other APCs release IL-12, which stimulates T cells to differentiate into Th1 cells. Th1 cells release IFN-γ to stimulate macrophages.

Helper T cells have CD4, which binds to MHC II on APCs.

Cytotoxic T cells

Kill virus-infected, neoplastic, and donor graft cells by inducing apoptosis.

Release cytotoxic granules containing preformed proteins (eg, perforin, granzyme B).

Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.

Regulatory T cells

Help maintain specific immune tolerance by suppressing CD4 and CD8 T-cell effector functions.

Identified by expression of CD3, CD4, CD25, and FOXP3.

Activated regulatory T cells (Tregs) produce anti-inflammatory cytokines (eg, IL-10, TGF-β).

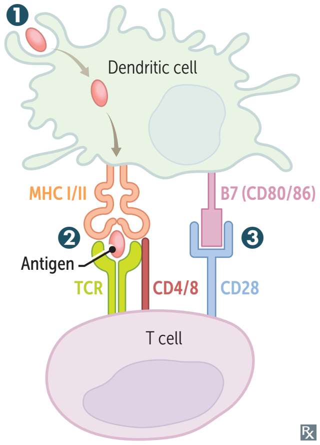
IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome—genetic deficiency of FOXP3 → autoimmunity. Characterized by enteropathy, endocrinopathy, nail dystrophy, dermatitis, and/or other autoimmune dermatologic conditions. Associated with diabetes in male infants.

T- and B-cell activation

APCs: B cells, dendritic cells, Langerhans cells, macrophages.
Two signals are required for T-cell activation, B-cell activation, and class switching.

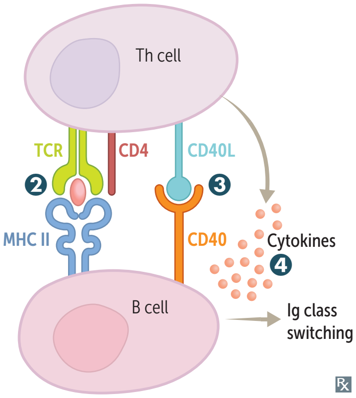
T-cell activation

❶ Dendritic cell (specialized APC) samples antigen, processes antigen, and migrates to the draining lymph node.
❷ T-cell activation (signal 1): antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous or cross-presented antigen is presented on MHC I to Tc (CD8+) cell.
❸ Proliferation and survival (signal 2): costimulatory signal via interaction of B7 protein on dendritic cell (CD80/86) and CD28 on naïve T cell.
❹ Th cell activates and produces cytokines. Tc cell activates and is able to recognize and kill virus-infected cell.


❶
Dendritic cell
MHC I/II
B7 (CD80/86)
❷
❸
Antigen
TCR
CD4/8
CD28
T cell

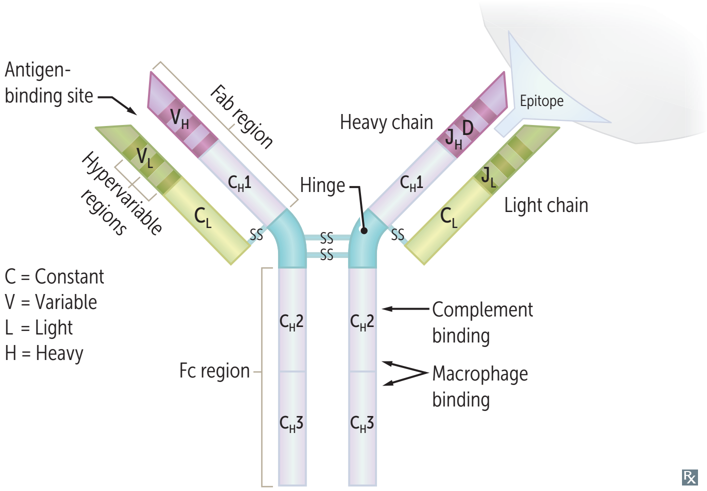
B-cell activation and class switching

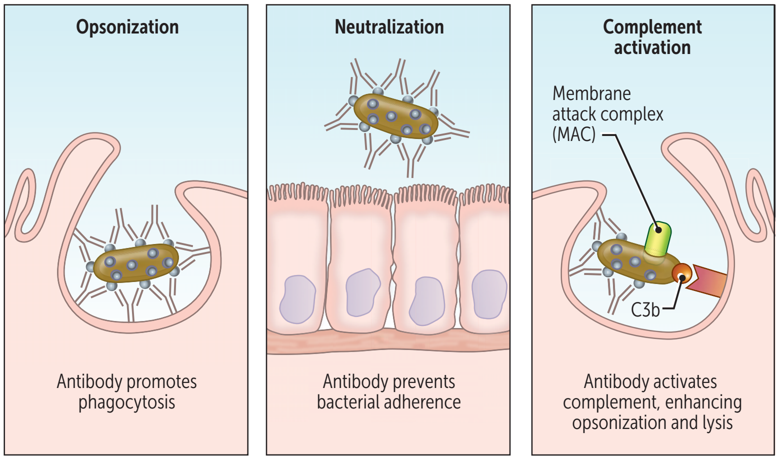
❶ Th-cell activation as above.
❷ B-cell receptor–mediated endocytosis; foreign antigen is presented on MHC II and recognized by TCR on Th cell.
❸ CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell.
❹ Th cell secretes cytokines that determine Ig class switching of B cell. B cell activates and undergoes class switching, affinity maturation, and antibody production.


Th cell
TCR
CD4
CD40L
❷
❸
MHC II
CD40
Cytokines
❹
B cell
Ig class switching

Antibody structure and function

Fab (containing the variable/hypervariable regions) consisting of light (L) and heavy (H) chains recognizes antigens. Fc region of IgM and IgG fixes complement. Heavy chain contributes to Fc and Fab regions. Light chain contributes only to Fab region.


Antigen-binding site
Fab region
V_H
V_L
Hypervariable regions
C_H1
C_L
SS
SS
SS
SS
Hinge
Heavy chain
J_H
D
Epitope
J_L
C_H1
C_L
Light chain
C = Constant
V = Variable
L = Light
H = Heavy
Fc region
C_H2
C_H2
C_H3
C_H3
Complement binding
Macrophage binding


Opsonization
Neutralization
Complement activation
Membrane attack complex (MAC)
C3b

Antibody promotes phagocytosis

Antibody prevents bacterial adherence

Antibody activates complement, enhancing opsonization and lysis

Fab:

- **F**ragment, **a**ntigen **b**inding
- Determines idiotype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell

Fc:

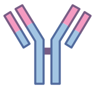
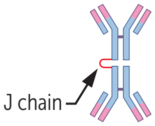
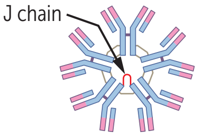
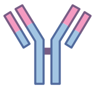
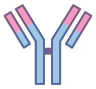
- **C**onstant
- **C**arboxy terminal
- **C**omplement binding
- **C**arbohydrate side chains
- Determines isotype (IgM, IgD, etc)

Generation of antibody diversity (antigen independent)

1. Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes
2. Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT)
3. Random combination of heavy chains with light chains

Generation of antibody specificity (antigen dependent)

4. Somatic hypermutation and affinity maturation (variable region)
5. Isotype switching (constant region)

Immunoglobulin isotypes	All isotypes can exist as monomers. Mature, naive B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; mediated by cytokines and CD40L) into plasma cells that secrete IgA, IgE, or IgG.
IgG 	Main antibody in 2° (**delayed**) response to an antigen. Most abundant isotype in serum. Fixes complement, crosses the placenta (provides infants with passive immunity), opsonizes bacteria, neutralizes bacterial toxins and viruses.
IgA 	Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement. Monomer (in circulation) or dimer (with J chain when secreted). Crosses epithelial cells by transcytosis. Produced in GI tract (eg, by Peyer patches) and protects against gut infections (eg, *Giardia*). Most produced antibody overall, but has lower serum concentrations. Released into secretions (tears, saliva, mucus) and breast milk. Picks up secretory component from epithelial cells, which protects the Fc portion from luminal proteases.
IgM 	Produced in the 1° (**immediate**) response to an antigen. Fixes complement but does not cross the placenta. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer with J chain when secreted. Pentamer enables avid binding to antigen while humoral response evolves.
IgD 	Unclear function. Found on surface of many B cells and in serum.
IgE 	Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Contributes to immunity to worms by activating eosinophils. Lowest concentration in serum.

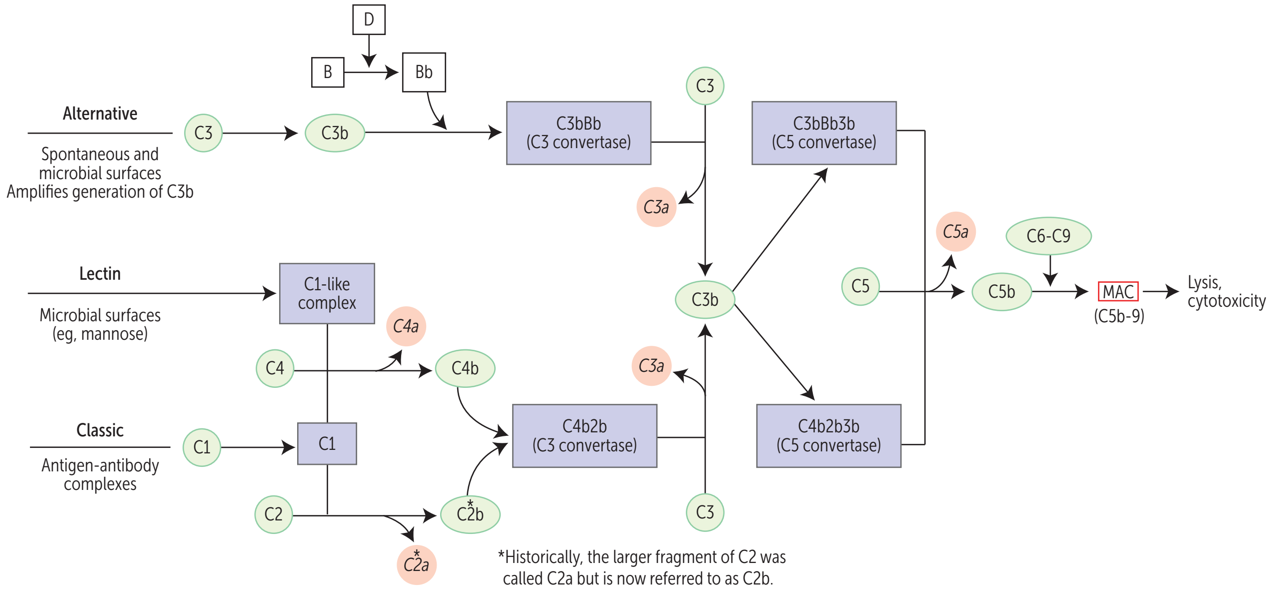
Antigen type and memory

Thymus-independent antigens	Antigens lacking a peptide component (eg, lipopolysaccharides from gram ⊖ bacteria); cannot be presented by MHC to T cells. Weakly immunogenic; vaccines often require boosters and adjuvants (eg, pneumococcal polysaccharide vaccine).
Thymus-dependent antigens	Antigens containing a protein component (eg, diphtheria vaccine). Class switching and immunologic memory occur as a result of direct contact of B cells with Th cells.

▶ IMMUNOLOGY—IMMUNE RESPONSES

Acute-phase reactants	Factors whose serum concentrations change significantly in response to inflammation; produced by the liver in both acute and chronic inflammatory states. Notably induced by IL-6.
POSITIVE (UPREGULATED)	
C-reactive protein	Opsonin; fixes complement and facilitates phagocytosis. Measured clinically as a nonspecific sign of ongoing inflammation.
Ferritin	Binds and sequesters iron to inhibit microbial iron scavenging.
Fibrinogen	Coagulation factor; promotes endothelial repair; correlates with ESR.
Hepcidin	↓ iron absorption (by degrading ferroportin) and ↓ iron release (from macrophages) → anemia of chronic disease.
Serum amyloid A	Prolonged elevation can lead to amyloidosis.
NEGATIVE (DOWNREGULATED)	
Albumin	Reduction conserves amino acids for positive reactants.
Transferrin	Internalized by macrophages to sequester iron.

Complement	System of hepatically synthesized plasma proteins that play a role in innate immunity and inflammation. Membrane attack complex (MAC) defends against gram ⊖ bacteria.	
ACTIVATION	**Classic** pathway—Ig**G** or Ig**M** mediated. Alternative pathway—microbe surface molecules. Lectin pathway—mannose or other sugars on microbe surface.	**GM** makes **classic** cars.
FUNCTIONS	C3b—opsonization. C3**a**, C4**a**, C5**a**—**a**naphylaxis. C5a—neutrophil chemotaxis. C5b-9—cytolysis by MAC.	C3**b** **b**inds **b**acteria.
	Opsonins—C3b and IgG are the two 1° opsonins in bacterial defense; enhance phagocytosis. C3b also helps clear immune complexes.	*Opsonin* (Greek) = to prepare for eating.
	Inhibitors—decay-accelerating factor (DAF, aka CD55) and C1 esterase inhibitor help prevent complement activation on self cells (eg, RBCs).	


D
B
Bb
Alternative
Spontaneous and microbial surfaces
Amplifies generation of C3b
C3
C3b
C3bBb (C3 convertase)
C3
C3bBb3b (C5 convertase)
C3a
C5a
C6-C9
Lectin
Microbial surfaces (eg, mannose)
C1-like complex
C4a
C3b
C5
C5b
MAC (C5b-9)
Lysis, cytotoxicity
C4
C4b
C3a
Classic
Antigen-antibody complexes
C1
C1
C4b2b (C3 convertase)
C4b2b3b (C5 convertase)
C2
C2b*
C3
C2a*

*Historically, the larger fragment of C2 was called C2a but is now referred to as C2b.

Complement disorders

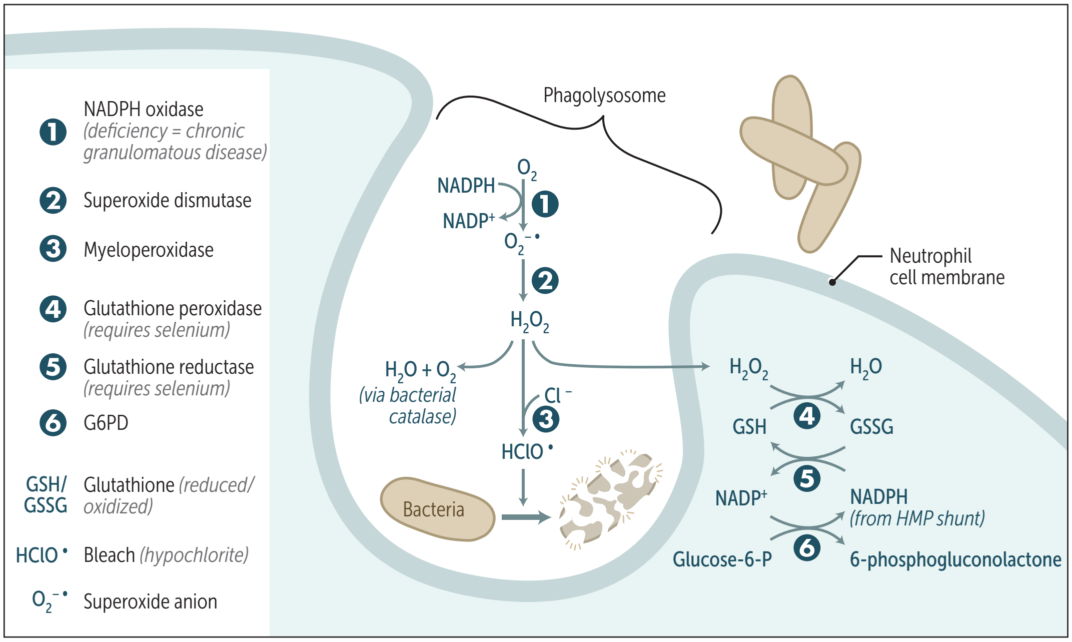
Complement protein deficiencies	
C3 deficiency	Increases risk of severe, recurrent pyogenic sinus and respiratory tract infections; ↑ susceptibility to type III hypersensitivity reactions.
C5–C9 deficiencies	Terminal complement deficiency increases susceptibility to recurrent *Neisseria* bacteremia.
Complement regulatory protein deficiencies	
C1 esterase inhibitor deficiency	Causes hereditary angioedema due to unregulated activation of kallikrein → ↑ bradykinin. Characterized by ↓ C4 levels. ACE inhibitors are contraindicated.
CD55 deficiency	Also called decay-accelerating factor (DAF) deficiency. Causes complement-mediated lysis of RBCs and paroxysmal nocturnal hemoglobinuria.

Important cytokines

SECRETED BY MACROPHAGES		
Interleukin-1	Causes fever, acute inflammation. Activates endothelium to express adhesion molecules. Induces chemokine secretion to recruit WBCs.	“**Hot T-bone** st**EAK**”: IL-1: fever (**hot**). IL-2: stimulates **T** cells. IL-3: stimulates **bone** marrow. IL-4: stimulates Ig**E** production. IL-5: stimulates Ig**A** production. IL-6: stimulates a**K**ute-phase protein production.
Interleukin-6	Causes fever and stimulates production of acute-phase proteins.	
Interleukin-8	Major chemotactic factor for neutrophils.	“**Clean up** on **aisle 8**.” Neutrophils are recruited by **IL-8** to **clear** infections.
Interleukin-12	Induces differentiation of T cells into Th1 cells. Activates NK cells.	
Tumor necrosis factor-α	Activates endothelium. Causes WBC recruitment, vascular leak.	Causes cachexia in malignancy. Maintains granulomas in TB. IL-1, IL-6, and TNF-α can mediate sepsis.
SECRETED BY ALL T CELLS		
Interleukin-2	Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.	
Interleukin-3	Supports growth and differentiation of bone marrow stem cells. Functions like GM-CSF.	
FROM Th1 CELLS		
Interferon-γ	Secreted by NK cells and T cells in response to antigen or IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens. Inhibits differentiation of Th2 cells.	Also activates NK cells to kill virus-infected cells. Increases MHC expression and antigen presentation by all cells.
FROM Th2 CELLS		
Interleukin-4	Induces differentiation of T cells into Th2 cells. Promotes growth of B cells. Enhances class switching to IgE and IgG.	
Interleukin-5	Promotes growth and differentiation of B cells. Enhances class switching to IgA. Stimulates growth and differentiation of eosinophils.	
Interleukin-10	Attenuates inflammatory response. Decreases expression of MHC class II and Th1 cytokines. Inhibits activated macrophages and dendritic cells. Also secreted by regulatory T cells.	TGF-**β** and IL-**10** **b**oth at**ten**uate the immune response.

Respiratory burst (oxidative burst)

Involves the activation of the phagocyte NADPH oxidase complex (eg, in neutrophils, monocytes), which utilizes O_2 as a substrate. Plays an important role in the immune response → rapid release of reactive oxygen species (ROS). NADPH plays a role in both the creation and neutralization of ROS. Myeloperoxidase is a blue-green heme-containing pigment that gives sputum its color.


❶ NADPH oxidase (deficiency = chronic granulomatous disease)
❷ Superoxide dismutase
❸ Myeloperoxidase
❹ Glutathione peroxidase (requires selenium)
❺ Glutathione reductase (requires selenium)
❻ G6PD
GSH/GSSG Glutathione (reduced/oxidized)
HClO• Bleach (hypochlorite)
$O_2^{-\bullet}$ Superoxide anion
Phagolysosome
O_2
NADPH
$NADP^+$
$O_2^{-\bullet}$
H_2O_2
$H_2O + O_2$ (via bacterial catalase)
Cl^-
HClO•
Bacteria
Neutrophil cell membrane
H_2O_2
H_2O
GSH
GSSG
$NADP^+$
NADPH (from HMP shunt)
Glucose-6-P
6-phosphogluconolactone

Phagocytes of patients with CGD can utilize H_2O_2 generated by invading organisms and convert it to ROS. Patients are at ↑ risk for infection by catalase ⊕ species (eg, *S aureus*, *Aspergillus*) capable of neutralizing their own H_2O_2, leaving phagocytes without ROS for fighting infections.

Pyocyanin of *P aeruginosa* functions to generate ROS to kill competing microbes. Lactoferrin is a protein found in secretory fluids and neutrophils that inhibits microbial growth via iron chelation.

Interferon-α and -β

A part of innate host defense against both RNA and DNA viruses. **Interfer**ons are glycoproteins synthesized by virus-infected cells that act locally on uninfected cells, "priming them" for viral defense by helping to degrade viral nucleic acid and protein.

Interfere with viruses.

Cell surface proteins	MHC I present on all nucleated cells (ie, not mature RBCs).	
T cells	TCR (binds antigen-MHC complex) CD3 (associated with TCR for signal transduction) CD28 (binds B7 on APC) CXCR4/CCR5 (co-receptors for HIV)	
Helper T cells	CD4, CD40L	
Cytotoxic T cells	CD8 CXCR4/CCR5	
Regulatory T cells	CD4, CD25	
B cells	Ig (binds antigen) CD19, CD20, CD21 (receptor for EBV), CD40 MHC II, B7	You can drink **B**eer at the **B**ar when you're **21**: **B** cells, Epstein-**B**arr virus, CD**21**.
Macrophages	CD14 (receptor for PAMPs, eg, LPS), CD40 CCR5 MHC II, B7 (CD80/86) Fc and C3b receptors (enhanced phagocytosis)	
NK cells	CD56 (suggestive marker for NK)	
Hematopoietic stem cells	CD34	
Anergy	State during which a cell cannot become activated by exposure to its antigen. T and B cells become anergic when exposed to their antigen without costimulatory signal (signal 2). Another mechanism of self-tolerance.	
Effects of bacterial toxins	Superantigens (*S pyogenes* and *S aureus*)—cross-link the β region of the T-cell receptor to the MHC class II on APCs. Can activate any CD4+ T cell → massive release of cytokines. Endotoxins/lipopolysaccharide (gram ⊖ bacteria)—directly stimulate macrophages by binding to endotoxin receptor TLR4/CD14; Th cells are not involved.	
Antigenic variation	Classic examples: ▪ Bacteria—*Salmonella* (2 flagellar variants), *Borrelia recurrentis* (relapsing fever), *N gonorrhoeae* (pilus protein) ▪ Viruses—influenza, HIV, HCV ▪ Parasites—trypanosomes	Some mechanisms for variation include DNA rearrangement and RNA segment reassortment (eg, influenza major shift) or protein mutations (eg, influenza minor drift).

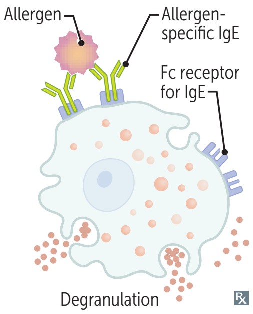
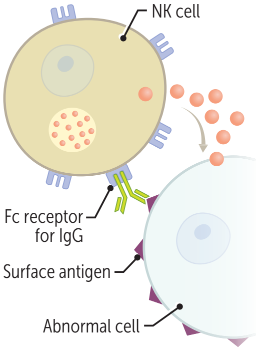
Passive vs active immunity

	Passive	Active
MEANS OF ACQUISITION	Receiving preformed antibodies	Exposure to foreign antigens
ONSET	Rapid	Slow
DURATION	Short span of antibodies (half-life = 3 weeks)	Long-lasting protection (memory)
EXAMPLES	IgA in breast milk, maternal IgG crossing placenta, antitoxin, humanized monoclonal antibody	Natural infection, vaccines, toxoid
NOTES	After exposure to **T**etanus toxin, **B**otulinum toxin, **H**BV, **V**aricella, **R**abies virus, or diphtheria antitoxin, unvaccinated patients are given preformed antibodies (passive)—"**T**o **B**e **H**ealed **V**ery **R**apidly"	Combined passive and active immunizations can be given for hepatitis B or rabies exposure

Vaccination

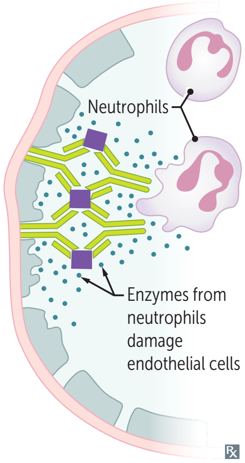
Induces an active immune response (humoral and/or cellular) to specific pathogens.

VACCINE TYPE	DESCRIPTION	PROS/CONS	EXAMPLES
Live attenuated vaccine	Microorganism loses its pathogenicity but retains capacity for transient growth within inoculated host. Induces **cellular and humoral responses**. MMR and varicella are live vaccines that can be given to patients with HIV who have a CD4 cell count > 200/mm^3.	Pro: induces strong, often lifelong immunity. Con: may revert to virulent form. Often contraindicated in pregnancy and immunodeficiency.	BCG, influenza (intranasal), measles, mumps, polio (Sabin), rotavirus, rubella, varicella, yellow fever.
Inactivated or killed vaccine	Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a **humoral response**.	Pro: safer than live vaccines. Con: weaker immune response; booster shots usually required.	**R**abies, **I**nfluenza (injection), **P**olio (Salk), hepatitis **A** ("**R.I.P. A**lways").

Hypersensitivity types	Four types: **A**naphylactic and **A**topic (type I), **C**ytotoxic (antibody mediated, type II), **I**mmune complex (type III), **D**elayed (cell mediated, type IV) (**ACID**).	
Type I  Allergen Allergen-specific IgE Fc receptor for IgE Degranulation	Anaphylactic and atopic—free antigen cross-links IgE on presensitized mast cells and basophils, triggering immediate release of vasoactive amines that act at postcapillary venules (ie, histamine). Reaction develops rapidly after antigen exposure because of preformed antibody. Delayed phase results from mast cells and basophils releasing cytokines that induce cellular inflammation.	**F**irst (type) and **F**ast (anaphylaxis). Types I, II, and III are all antibody mediated. Test: skin test or blood test (ELISA) for allergen-specific IgE. Example: ▪ Anaphylaxis (eg, food, drug, or bee sting allergies)
Type II  NK cell Fc receptor for IgG Surface antigen Abnormal cell **Antibody-dependent cellular cytotoxicity**	Antibodies bind to cell-surface antigens → cellular destruction, inflammation, and cellular dysfunction.	**Direct** Coombs test—detects antibodies attached **direct**ly to the RBC surface. Indirect Coombs test—detects presence of unbound antibodies in the serum
	Cellular destruction: cell is opsonized (coated) by antibodies, leading to either: ▪ Phagocytosis and/or activation of complement system. ▪ NK cell killing (antibody-dependent cellular cytotoxicity).	Examples: ▪ Autoimmune-hemolytic anemia ▪ Immune thrombocytopenic purpura ▪ Transfusion reactions ▪ Hemolytic disease of the newborn
	Inflammation—binding of antibodies to cell surfaces → activation of complement system and Fc receptor-mediated inflammation.	Examples: ▪ Goodpasture syndrome ▪ Rheumatic fever ▪ Hyperacute transplant rejection
	Cellular dysfunction—antibodies bind to cell surface receptors → abnormal blockade or activation of downstream process.	Examples: ▪ Myasthenia gravis ▪ Graves disease

Hypersensitivity types *(continued)*

Type III



Immune complex—antigen-antibody (IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.

Can be associated with vasculitis and systemic manifestations.

In type III reaction, imagine an immune complex as 3 things stuck together: antigen-antibody-complement.

Examples:

- SLE
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis

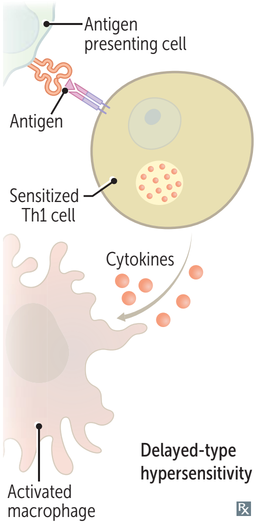
Serum sickness—an immune complex disease in which antibodies to foreign proteins are produced (takes 5 days). Immune complexes form and are deposited in membranes, where they fix complement (leads to tissue damage). More common than Arthus reaction.

Most serum sickness is now caused by drugs (not serum) acting as haptens. Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 5–10 days after antigen exposure.

Arthus reaction—a local subacute antibody-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin. Characterized by edema, necrosis, and activation of complement.

Antigen-antibody complexes cause the Arthus reaction.

Type IV



Two mechanisms, each involving T cells:

1. Direct cell cytotoxicity: CD8+ cytotoxic T cells kill targeted cells.
2. Delayed-type hypersensitivity: sensitized CD4+ helper T cells encounter antigen and release cytokines → inflammation and macrophage activation.

Response does not involve antibodies (vs types I, II, and III).

Example:

- Type 1 diabetes mellitus

Examples:

- Contact dermatitis (eg, poison ivy, nickel allergy)
- Graft-versus-host disease

Tests: PPD, patch test.

4T's: T cells, Transplant rejections, TB skin tests, Touching (contact dermatitis).

Fourth (type) and last (delayed).

Blood transfusion reactions

TYPE	PATHOGENESIS	CLINICAL PRESENTATION	TIMING
Allergic/anaphylactic reaction	Type 1 hypersensitivity reaction against plasma proteins in transfused blood. IgA-deficient individuals must receive blood products without IgA.	Urticaria, pruritus, fever, wheezing, hypotension, respiratory arrest, shock.	Within minutes to 2–3 hours
Febrile nonhemolytic transfusion reaction	Type II hypersensitivity reaction. Host antibodies against donor HLA antigens and WBCs.	Fever, headaches, chills, flushing.	Within 1–6 hours
Acute hemolytic transfusion reaction	Type II hypersensitivity reaction. Intravascular hemolysis (ABO blood group incompatibility) or extravascular hemolysis (host antibody reaction against foreign antigen on donor RBCs).	Fever, hypotension, tachypnea, tachycardia, flank pain, hemoglobinuria (intravascular hemolysis), jaundice (extravascular).	Within 1 hour
Transfusion-related acute lung injury	Donor anti-leukocyte antibodies against recipient neutrophils and pulmonary endothelial cells.	Respiratory distress and noncardiogenic pulmonary edema.	Within 6 hours

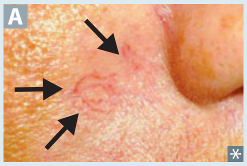
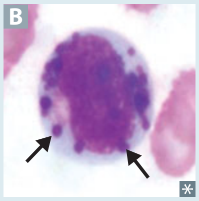
Autoantibodies

AUTOANTIBODY	ASSOCIATED DISORDER
Anti-ACh receptor	Myasthenia gravis
Anti-glomerular basement membrane	Goodpasture syndrome
Anti-β_2 glycoprotein	Antiphospholipid syndrome
Anticardiolipin, lupus anticoagulant	SLE, antiphospholipid syndrome
Anticentromere	Limited scleroderma (CREST syndrome)
Anti-desmoglein (anti-desmosome)	Pemphigus vulgaris
Anti-glutamic acid decarboxylase, islet cell cytoplasmic antibodies	Type 1 diabetes mellitus
Anti-hemidesmosome	Bullous pemphigoid
Antisynthetase (eg, anti-Jo-1), anti-SRP, anti-helicase (anti-Mi-2)	Polymyositis, dermatomyositis
Antimicrosomal, antithyroglobulin, anti-thyroid peroxidase	Hashimoto thyroiditis
Antimitochondrial	1° biliary cirrhosis
Antiparietal cell, anti-intrinsic factor	Pernicious anemia
Antiphospholipase A_2 receptor	1° membranous nephropathy
Anti-Scl-70 (anti-DNA topoisomerase I)	Scleroderma (diffuse)
Anti-smooth muscle	Autoimmune hepatitis type 1
Anti-SSA, anti-SSB (anti-Ro, anti-La)	Sjögren syndrome
Anti-TSH receptor	Graves disease
Anti-presynaptic voltage-gated calcium channel	Lambert-Eaton myasthenic syndrome
IgA anti-endomysial, IgA anti-tissue transglutaminase	Celiac disease
MPO-ANCA/p-ANCA	Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), ulcerative colitis
PR3-ANCA/c-ANCA	Granulomatosis with polyangiitis (Wegener)
Rheumatoid factor (IgM antibody against IgG Fc region), anti-CCP (more specific)	Rheumatoid arthritis
Antinuclear (ANA)	Nonspecific screening antibody, often associated with SLE
Anti-dsDNA, anti-Smith	SLE
Anti-histone	Drug-induced lupus
Anti-U1 RNP (ribonucleoprotein)	Mixed connective tissue disease

Immunodeficiencies

DISEASE	DEFECT	PRESENTATION	FINDINGS
B-cell disorders			
X-linked (Bruton) agammaglobulinemia	Defect in *BTK*, a tyrosine kinase gene → no B-cell maturation. X-linked recessive (↑ in Boys).	Recurrent bacterial and enteroviral infections after 6 months (↓ maternal IgG).	Absent B cells in peripheral blood, ↓ Ig of all classes. Absent/scanty lymph nodes and tonsils. Live vaccines contraindicated.
Selective IgA deficiency	Unknown. Most common 1° immunodeficiency.	Majority Asymptomatic. Can see Airway and GI infections, Autoimmune disease, Atopy, Anaphylaxis to IgA-containing products.	↓ IgA with normal IgG, IgM levels. ↑ susceptibility to giardiasis.
Common variable immunodeficiency	Defect in B-cell differentiation. Many causes.	Usually presents after age 2 and may be considerably delayed; ↑ risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infections.	↓ plasma cells, ↓ immunoglobulins.
T-cell disorders			
Thymic aplasia (DiGeorge syndrome)	22q11 deletion; failure to develop 3rd and 4th pharyngeal pouches → absent thymus and parathyroids.	Tetany (hypocalcemia), recurrent viral/fungal infections (T-cell deficiency), conotruncal abnormalities (eg, tetralogy of Fallot, truncus arteriosus).	↓ T cells, ↓ PTH, ↓ Ca^{2+}. Absent thymic shadow on CXR.
IL-12 receptor deficiency	↓ Th1 response. Autosomal recessive.	Disseminated mycobacterial and fungal infections; may present after administration of BCG vaccine.	↓ IFN-γ.
Autosomal dominant hyper-IgE syndrome (Job syndrome)	Deficiency of Th17 cells due to *STAT3* mutation → impaired recruitment of neutrophils to sites of infection.	FATED: coarse Facies, cold (noninflamed) staphylococcal Abscesses, retained primary Teeth, ↑ IgE, Dermatologic problems (eczema). Bone fractures from minor trauma.	↑ IgE, ↓ IFN-γ. ↑ eosinophils.
Chronic mucocutaneous candidiasis	T-cell dysfunction. Many causes.	Noninvasive *Candida albicans* infections of skin and mucous membranes.	Absent in vitro T-cell proliferation in response to *Candida* antigens. Absent cutaneous reaction to *Candida* antigens.

Immunodeficiencies *(continued)*

DISEASE	DEFECT	PRESENTATION	FINDINGS
B- and T-cell disorders			
Severe combined immunodeficiency	Several types including defective IL-2R gamma chain (most common, X-linked), adenosine deaminase deficiency (autosomal recessive).	Failure to thrive, chronic diarrhea, thrush. Recurrent viral, bacterial, fungal, and protozoal infections. Treatment: avoid live vaccines, give antimicrobial prophylaxis and IVIG; bone marrow transplant curative (no concern for rejection).	↓ T-cell receptor excision circles (TRECs). Absence of thymic shadow (CXR), germinal centers (lymph node biopsy), and T cells (flow cytometry).
Ataxia-telangiectasia 	Defects in *ATM* gene → failure to repair DNA double strand breaks → cell cycle arrest.	Triad: cerebellar defects (**A**taxia), spider **A**ngiomas (telangiectasia **A**), Ig**A** deficiency.	↑ AFP. ↓ IgA, IgG, and IgE. Lymphopenia, cerebellar atrophy. ↑ risk of lymphoma and leukemia.
Hyper-IgM syndrome	Most commonly due to defective CD40L on Th cells → class switching defect; X-linked recessive.	Severe pyogenic infections early in life; opportunistic infection with *Pneumocystis*, *Cryptosporidium*, CMV.	Normal or ↑ IgM. ↓↓ IgG, IgA, IgE. Failure to make germinal centers.
Wiskott-Aldrich syndrome	Mutation in *WASp* gene; leukocytes and platelets unable to reorganize actin cytoskeleton → defective antigen presentation. X-linked recessive.	**WATER**: **W**iskott-**A**ldrich: **T**hrombocytopenia, **E**czema, **R**ecurrent (pyogenic) infections. ↑ risk of autoimmune disease and malignancy.	↓ to normal IgG, IgM. ↑ IgE, IgA. Fewer and smaller platelets.
Phagocyte dysfunction			
Leukocyte adhesion deficiency (type 1)	Defect in LFA-1 integrin (CD18) protein on phagocytes; impaired migration and chemotaxis; autosomal recessive.	Recurrent skin and mucosal bacterial infections, absent pus, impaired wound healing, delayed (> 30 days) separation of umbilical cord.	↑ neutrophils. Absence of neutrophils at infection sites.
Chédiak-Higashi syndrome 	Defect in lysosomal trafficking regulator gene (*LYST*). Microtubule dysfunction in phagosome-lysosome fusion; autosomal recessive.	Recurrent pyogenic infections by staphylococci and streptococci, partial albinism, peripheral neuropathy, progressive neurodegeneration, infiltrative lymphohistiocytosis.	Giant granules (**B**, arrows) in granulocytes and platelets. Pancytopenia. Mild coagulation defects.
Chronic granulomatous disease	Defect of NADPH oxidase → ↓ reactive oxygen species (eg, superoxide) and ↓ respiratory burst in neutrophils; X-linked recessive most common.	↑ susceptibility to catalase ⊕ organisms.	Abnormal dihydrorhodamine (flow cytometry) test (↓ green fluorescence). Nitroblue tetrazolium dye reduction test (obsolete) fails to turn blue.

Infections in immunodeficiency

PATHOGEN	↓ T CELLS	↓ B CELLS	↓ GRANULOCYTES	↓ COMPLEMENT
Bacteria	Sepsis	Encapsulated (Please **SHINE** my **SKiS**): ***P**seudomonas aeruginosa*, ***S**treptococcus pneumoniae*, ***H**aemophilus **I**nfluenzae* type B, ***N**eisseria meningitidis*, ***E**scherichia coli*, ***S**almonella*, ***K**lebsiella pneumoniae*, Group B ***S**treptococcus*	*Staphylococcus*, *Burkholderia cepacia*, *Pseudomonas aeruginosa*, *Serratia*, *Nocardia*	Encapsulated species with early component deficiencies *Neisseria* with late complement (C5–C9) deficiencies
Viruses	CMV, EBV, JC virus, VZV, chronic infection with respiratory/GI viruses	Enteroviral encephalitis, poliovirus (live vaccine contraindicated)	N/A	N/A
Fungi/parasites	*Candida* (local), PCP, *Cryptococcus*	GI giardiasis (no IgA)	*Candida* (systemic), *Aspergillus*, *Mucor*	N/A

Note: **B**-cell deficiencies tend to produce recurrent **b**acterial infections, whereas T-cell deficiencies produce more fungal and viral infections.

Grafts

Autograft	From self.
Syngeneic graft (isograft)	From identical twin or clone.
Allograft	From nonidentical individual of same species.
Xenograft	From different species.

Transplant rejection

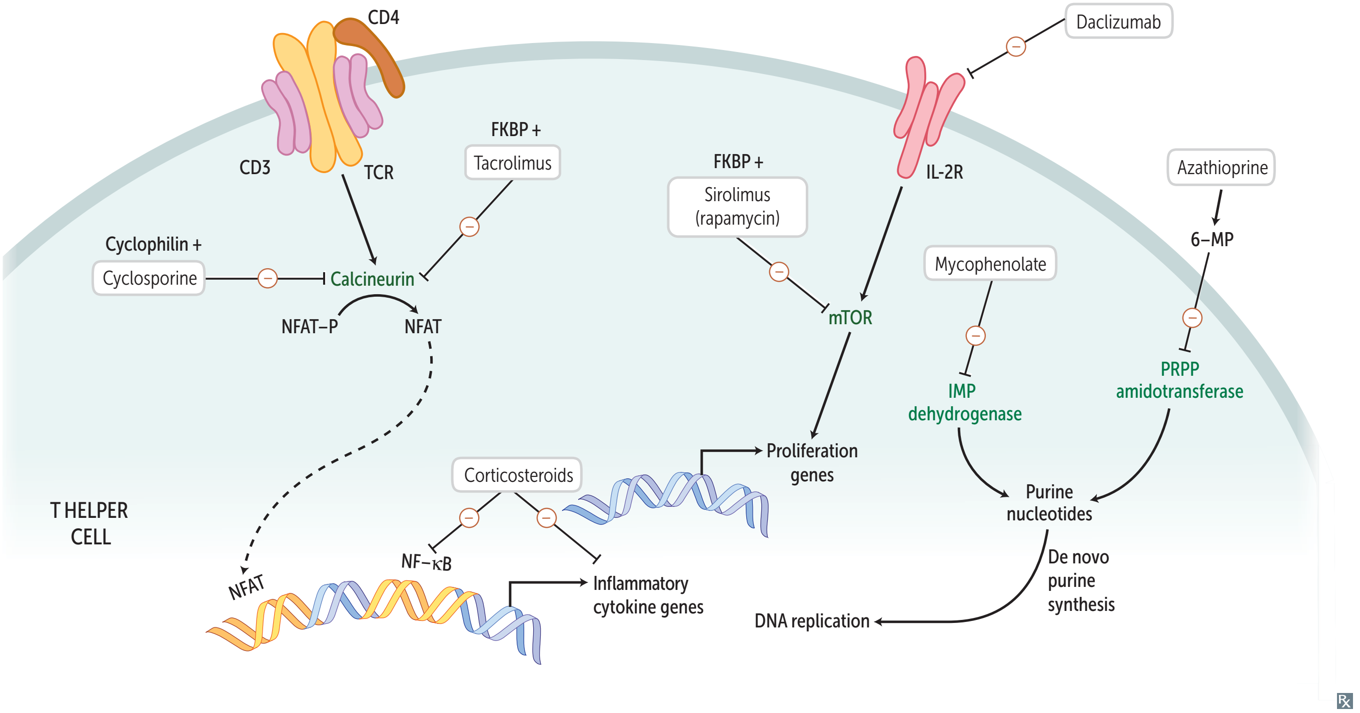
TYPE OF REJECTION	ONSET	PATHOGENESIS	FEATURES
Hyperacute	Within minutes	Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement.	Widespread thrombosis of graft vessels → ischemia/necrosis. Graft must be removed.
Acute	Weeks to months	Cellular: CD8+ T cells activated against donor MHCs (type IV hypersensitivity reaction). Humoral: similar to hyperacute, except antibodies develop after transplant.	Vasculitis of graft vessels with dense interstitial lymphocytic infiltrate. Prevent/reverse with immunosuppressants.
Chronic	Months to years	CD4+ T cells respond to recipient APCs presenting donor peptides, including allogeneic MHC. Both cellular and humoral components (type II and IV hypersensitivity reactions).	Recipient T cells react and secrete cytokines → proliferation of vascular smooth muscle, parenchymal atrophy, interstitial fibrosis. Dominated by arteriosclerosis. Organ-specific examples: ▪ Bronchiolitis obliterans (lung) ▪ Accelerated atherosclerosis (heart) ▪ Chronic graft nephropathy (kidney) ▪ Vanishing bile duct syndrome (liver)
Graft-versus-host disease	Varies	Grafted immunocompetent T cells proliferate in the immunocompromised host and reject host cells with "foreign" proteins → severe organ dysfunction. Type IV hypersensitivity reaction.	Maculopapular rash, jaundice, diarrhea, hepatosplenomegaly. Usually in bone marrow and liver transplants (rich in lymphocytes). Potentially beneficial in bone marrow transplant for leukemia (graft-versus-tumor effect).

▸ IMMUNOLOGY—IMMUNOSUPPRESSANTS

Immunosuppressants Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by suppressing cellular immunity (used as prophylaxis). Frequently combined to achieve greater efficacy with ↓ toxicity. Chronic suppression ↑ risk of infection and malignancy.

DRUG	MECHANISM	OTHER USE	TOXICITY	NOTES
Cyclosporine	Calcineurin inhibitor; binds **cyclo**philin. Blocks T-cell activation by **preventing IL-2 transcription**.	Psoriasis, rheumatoid arthritis.	**Nephrotoxicity**, hypertension, hyperlipidemia, neurotoxicity, gingival hyperplasia, hirsutism.	Both calcineurin inhibitors are highly nephrotoxic.
Tacrolimus (FK506)	Calcineurin inhibitor; binds **FK506** binding protein (FKBP). Blocks T-cell activation by **preventing IL-2 transcription**.		Similar to cyclosporine, ↑ risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism.	
Sirolimus (Rapamycin)	**m**TO**R** inhibitor; binds FKBP. Blocks T-cell activation and B-cell differentiation by **preventing response to IL-2**.	Kidney transplant rejection prophylaxis specifically.	"Pan**Sir**topenia" (pancytopenia), insulin resistance, hyperlipidemia; **not nephrotoxic**.	Kidney "**sir**-vives." Synergistic with cyclosporine. Also used in drug-eluting stents.
Basiliximab	Monoclonal antibody; blocks IL-2R.		Edema, hypertension, tremor.	
Azathioprine	Antimetabolite precursor of 6-mercapto**purine**. Inhibits lymphocyte proliferation by blocking nucleotide synthesis.	Rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions.	Pancytopenia.	6-MP degraded by xanthine oxidase; toxicity ↑ by allopurinol. Pronounce "azathio-**purine**."
Mycophenolate mofetil	Reversibly inhibits IMP dehydrogenase, preventing purine synthesis of B and T cells.	Lupus nephritis.	GI upset, pancytopenia, hypertension, hyperglycemia. Less nephrotoxic and neurotoxic.	Associated with invasive CMV infection.
Corticosteroids	Inhibit NF-κB. Suppress both B- and T-cell function by ↓ transcription of many cytokines. Induce T cell apoptosis.	Many autoimmune and inflammatory disorders, adrenal insufficiency, asthma, CLL, non-Hodgkin lymphoma.	Cushing syndrome, osteoporosis, hyperglycemia, diabetes, amenorrhea, adrenocortical atrophy, peptic ulcers, psychosis, cataracts, avascular necrosis (femoral head).	Demargination of WBCs causes artificial leukocytosis. Adrenal insufficiency may develop if drug is stopped abruptly after chronic use.

Immunosuppression targets


CD4
Daclizumab
CD3
TCR
FKBP +
Tacrolimus
FKBP +
Sirolimus (rapamycin)
IL-2R
Azathioprine
6–MP
Cyclophilin +
Cyclosporine
Calcineurin
NFAT–P
NFAT
Mycophenolate
mTOR
PRPP amidotransferase
IMP dehydrogenase
Proliferation genes
Corticosteroids
Purine nucleotides
T HELPER CELL
NF–κB
NFAT
Inflammatory cytokine genes
De novo purine synthesis
DNA replication

Recombinant cytokines and clinical uses

AGENT	CLINICAL USES
Aldesleukin (IL-2)	Renal cell carcinoma, metastatic melanoma
Epoetin alfa (erythropoietin)	Anemias (especially in renal failure)
Fil**gra**stim (G-CSF)	Recovery of bone marrow and WBC counts by **gra**nulocyte stimulation
Sar**gramostim** (GM-CSF)	Recovery of bone marrow and WBC counts by **gra**nulocyte and **mo**nocyte stimulation
IFN-α	Chronic hepatitis B and C, Kaposi sarcoma, malignant melanoma, hairy cell leukemia, condyloma acuminata, renal cell carcinoma
IFN-β	Multiple sclerosis
IFN-**γ**	Chronic **gra**nulomatous disease
Romiplostim (thrombopoietin analog), eltrombopag (thrombopoietin receptor agonist)	Thrombocytopenia
Oprelvekin (IL-11)	Thrombocytopenia

Therapeutic antibodies

AGENT	TARGET	CLINICAL USE	NOTES
Cancer therapy			
Alemtuzumab	CD52	CLL, MS	"Alymtuzumab"—chronic lymphocytic leukemia
Bevacizumab	VEGF	Colorectal cancer, renal cell carcinoma, non-small cell lung cancer	
Cetuximab	EGFR	Stage IV colorectal cancer, head and neck cancer	
Rituximab	CD20	B-cell non-Hodgkin lymphoma, CLL, rheumatoid arthritis, ITP	
Trastuzumab	HER2/neu	Breast cancer, gastric cancer	HER2—"tras2zumab"
Autoimmune disease therapy			
Adalimumab, certolizumab, golimumab, infliximab	Soluble TNF-α	IBD, rheumatoid arthritis, ankylosing spondylitis, psoriasis	Etanercept is a decoy TNF-α receptor and not a monoclonal antibody
Daclizumab	CD25 (part of IL-2 receptor)	Relapsing multiple sclerosis	
Eculizumab	Complement protein C5	Paroxysmal nocturnal hemoglobinuria	
Natalizumab	α4-integrin	Multiple sclerosis, Crohn disease	α4-integrin: WBC adhesion Risk of PML in patients with JC virus
Ustekinumab	IL-12/IL-23	Psoriasis, psoriatic arthritis	
Other applications			
Abciximab	Platelet glycoproteins IIb/IIIa	Antiplatelet agent for prevention of ischemic complications in patients undergoing percutaneous coronary intervention	IIb times IIIa equals "absiximab"
Denosumab	RANKL	Osteoporosis; inhibits osteoclast maturation (mimics osteoprotegerin)	Denosumab affects osteoclasts
Digoxin immune Fab	Digoxin	Antidote for digoxin toxicity	
Omalizumab	IgE	Refractory allergic asthma; prevents IgE binding to FcεRI	
Palivizumab	RSV F protein	RSV prophylaxis for high-risk infants	PaliVIzumab—VIrus
Ranibizumab, bevacizumab	VEGF	Neovascular age-related macular degeneration, proliferative diabetic retinopathy and macular edema	

HIGH-YIELD PRINCIPLES IN

Microbiology

"Support bacteria. They're the only culture some people have."

—Steven Wright

"What lies behind us and what lies ahead of us are tiny matters compared to what lies within us."

—Henry S. Haskins

"Infectious disease is merely a disagreeable instance of a widely prevalent tendency of all living creatures to save themselves the bother of building, by their own efforts, the things they require."

—Hans Zinsser

- Basic Bacteriology 120
- Clinical Bacteriology 130
- Mycology 147
- Parasitology 151
- Virology 158
- Systems 174
- Antimicrobials 183

Microbiology questions on the Step 1 exam often require two (or more) steps: Given a certain clinical presentation, you will first need to identify the most likely causative organism, and you will then need to provide an answer regarding some feature of that organism. For example, a description of a child with fever and a petechial rash will be followed by a question that reads, "From what site does the responsible organism usually enter the blood?"

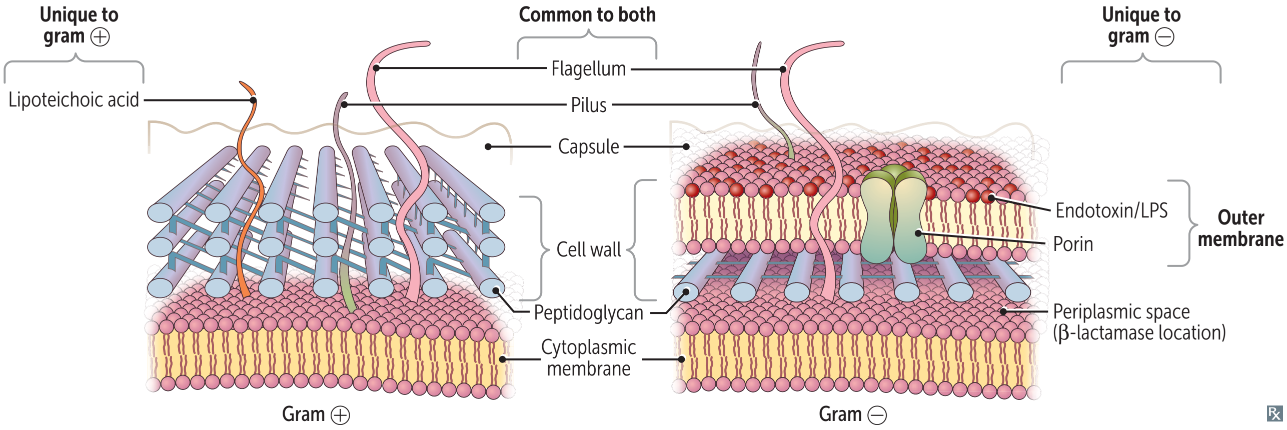
This section therefore presents organisms in two major ways: in individual microbial "profiles" and in the context of the systems they infect and the clinical presentations they produce. You should become familiar with both formats. When reviewing the systems approach, remind yourself of the features of each microbe by returning to the individual profiles. Also be sure to memorize the laboratory characteristics that allow you to identify microbes.

▸ MICROBIOLOGY—BASIC BACTERIOLOGY

Bacterial structures

STRUCTURE	CHEMICAL COMPOSITION	FUNCTION
Appendages		
Flagellum	Proteins.	Motility.
Pilus/fimbria	Glycoprotein.	Mediate adherence of bacteria to cell surface; sex pilus forms during conjugation.
Specialized structures		
Spore	Keratin-like coat; dipicolinic acid; peptidoglycan, DNA.	Gram ⊕ only. Survival: resist dehydration, heat, chemicals.
Cell envelope		
Capsule	Organized, discrete polysaccharide layer (except poly-ᴅ-glutamate on *B anthracis*).	Protects against phagocytosis.
Glycocalyx	Loose network of polysaccharides.	Mediates adherence to surfaces, especially foreign surfaces (eg, indwelling catheters).
Outer membrane	Outer leaflet: contains endotoxin (LPS/LOS). Embedded proteins: porins and other outer membrane proteins (OMPs) Inner leaflet: phospholipids.	Gram ⊖ only. Endotoxin: lipid A induces TNF and IL-1; antigenic O polysaccharide component. Most OMPs are antigenic. Porins: transport across outer membrane.
Periplasm	Space between cytoplasmic membrane and outer membrane in gram ⊖ bacteria. (Peptidoglycan in middle.)	Accumulates components exiting gram ⊖ cells, including hydrolytic enzymes (eg, β-lactamases).
Cell wall	Peptidoglycan is a sugar backbone with peptide side chains cross-linked by transpeptidase.	Net-like structure gives rigid support, protects against osmotic pressure damage.
Cytoplasmic membrane	Phospholipid bilayer sac with embedded proteins (eg, penicillin-binding proteins [PBPs]) and other enzymes. Lipoteichoic acids (gram ⊕ only) extend from membrane to exterior.	Site of oxidative and transport enzymes; PBPs involved in cell wall synthesis. Lipoteichoic acids induce TNF-α and IL-1.

Cell walls

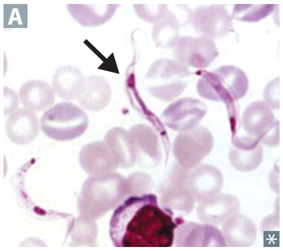

Unique to gram ⊕
Common to both
Unique to gram ⊖
Lipoteichoic acid
Flagellum
Pilus
Capsule
Cell wall
Peptidoglycan
Cytoplasmic membrane
Endotoxin/LPS
Porin
Outer membrane
Periplasmic space (β-lactamase location)
Gram ⊕
Gram ⊖

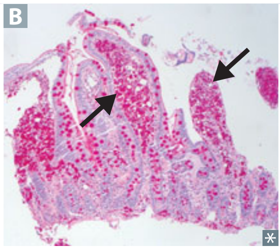
Bacterial taxonomy

MORPHOLOGY	Gram ⊕ examples	Gram ⊖ examples
Spherical (coccus)	*Staphylococcus* (clusters) *Streptococcus* (chains or pairs) *Enterococcus* (pairs or short chains)	*Moraxella catarrhalis* *Neisseria*
Rod (bacillus)	*Bacillus* *Clostridium* *Corynebacterium* *Gardnerella* (gram variable) *Lactobacillus* *Listeria* *Mycobacterium* (acid fast) *Propionibacterium*	Enterics: ▪ *Bacteroides* ▪ *Campylobacter* ▪ *E coli* ▪ *Enterobacter* ▪ *Fusobacterium* ▪ *Helicobacter* ▪ *Klebsiella* ▪ *Proteus* ▪ *Pseudomonas* ▪ *Salmonella* ▪ *Serratia* ▪ *Shigella* ▪ *Vibrio* ▪ *Yersinia* Respiratory: ▪ *Bordetella* ▪ *Burkholderia cepacia* ▪ *Haemophilus* (pleomorphic) ▪ *Legionella* (silver stain) Zoonotic: ▪ *Bartonella* ▪ *Brucella* ▪ *Francisella* ▪ *Pasteurella*
Branching filamentous	*Actinomyces* *Nocardia* (weakly acid fast)	
Pleomorphic (no cell wall)		*Anaplasma*, *Ehrlichia* *Chlamydiae* (Giemsa) *Rickettsiae* (Giemsa) *Mycoplasma* (contains sterols, which do not Gram stain)
Spiral		Spirochetes: ▪ *Borrelia* (Giemsa) ▪ *Leptospira* ▪ *Treponema*

Stains

Gram stain	First-line lab test in bacterial identification. Bacteria with thick peptidoglycan layer retain crystal violet dye (gram ⊕); bacteria with thin peptidoglycan layer turn red or pink (gram ⊖) with counterstain. These bugs do not Gram stain well (**T**hese **L**ittle **M**icrobes **M**ay **U**nfortunately **L**ack **R**eal **C**olor **B**ut **A**re **E**verywhere).	
	Treponema, *__L__eptospira*	Too thin to be visualized.
	Mycobacteria	Cell wall has high lipid content.
	__M__ycoplasma, *__U__reaplasma*	No cell wall.
	__L__egionella, *__R__ickettsia*, *__C__hlamydia*, *__B__artonella*, *__A__naplasma*, *__E__hrlichia*	Primarily intracellular; also, *Chlamydia* lack classic peptidoglycan because of ↓ muramic acid.
Giemsa stain	*__C__hlamydia*, *__B__orrelia*, *__R__ickettsia*, **T**rypanosomes A, *__P__lasmodium*	**C**ertain **B**ugs **R**eally **T**ry my **P**atience.
Periodic acid–Schiff stain	Stains **glycogen**, mucopolysaccharides; used to diagnose Whipple disease (*Tropheryma whipplei* B)	**PaS**s the **sugar**.
Ziehl-Neelsen stain (carbol fuchsin)	Acid-fast bacteria (eg, *Mycobacteria* C, *Nocardia*; stains mycolic acid in cell wall); protozoa (eg, *Cryptosporidium* oocysts)	Current standard of care is auramine-rhodamine stain for screening (inexpensive, more sensitive but less specific).
India ink stain	*Cryptococcus neoformans* D; mucicarmine can also be used to stain thick polysaccharide capsule red	
Silver stain	Fungi (eg, *Coccidioides* E, *Pneumocystis jirovecii*), *Legionella*, *Helicobacter pylori*	
Fluorescent antibody stain	Used to identify many bacteria and viruses.	Example is FTA-ABS for syphilis.


A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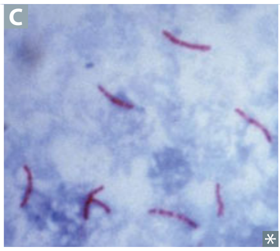
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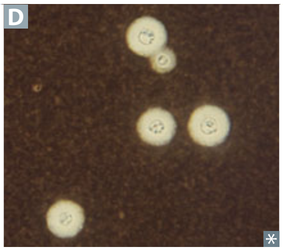
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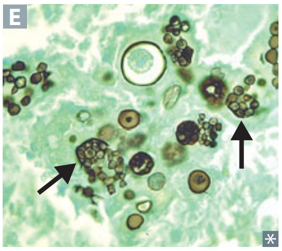

E

Properties of growth media

The same type of media can possess both (or neither) of these properties.

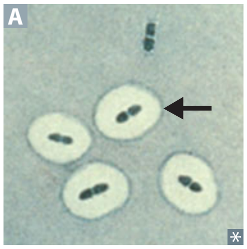
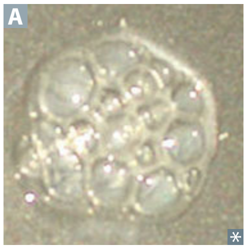
Selective media	Favors the growth of particular organism while preventing growth of other organisms, eg, Thayer-Martin agar contains antibiotics that allow the selective growth of *Neisseria* by inhibiting the growth of other sensitive organisms.
Indicator (differential) media	Yields a color change in response to the metabolism of certain organisms, eg, MacConkey agar contains a pH indicator; a lactose fermenter like *E coli* will convert lactose to acidic metabolites → color change.

Special culture requirements

BUG	MEDIA USED FOR ISOLATION	MEDIA CONTENTS/OTHER
H influenzae	Chocolate agar	Factors V (NAD$^+$) and X (hematin)
N gonorrhoeae, *N meningitidis*	Thayer-Martin agar	Selectively favors growth of *Neisseria* by inhibiting growth of gram ⊕ organisms with **V**ancomycin, gram ⊖ organisms except *Neisseria* with **T**rimethoprim and **C**olistin, and fungi with **N**ystatin **V**ery **T**ypically **C**ultures ***N**eisseria*
B pertussis	Bordet-Gengou agar (**Bordet** for ***Bordet**ella*) Regan-Lowe medium	Potato extract Charcoal, blood, and antibiotic
C diphtheriae	Tellurite agar, Löffler medium	
M tuberculosis	Löwenstein-Jensen agar	
M pneumoniae	Eaton agar	Requires cholesterol
Lactose-fermenting enterics	MacConkey agar	Fermentation produces acid, causing colonies to turn pink
E coli	Eosin–methylene blue (EMB) agar	Colonies with green metallic sheen
Legionella	Charcoal yeast extract agar buffered with cysteine and iron	
Fungi	**Sab**ouraud agar	“**Sab**’s a **fun guy**!”

Aerobes	Use an O$_2$-dependent system to generate ATP. Examples include ***N**ocardia*, ***P**seudomonas aeruginosa*, and ***M**yco**B**acterium tuberculosis*. Reactivation of *M tuberculosis* (eg, after immunocompromise or TNF-α inhibitor use) has a predilection for the apices of the lung.	**N**agging **P**ests **M**ust **B**reathe.
Anaerobes	Examples include ***Clostridium***, ***Bacteroides***, ***Fusobacterium***, and ***Actinomyces***. They lack catalase and/or superoxide dismutase and are thus susceptible to oxidative damage. Generally foul smelling (short-chain fatty acids), are difficult to culture, and produce gas in tissue (CO$_2$ and H$_2$).	Anaerobes **C**an’t **B**reathe **F**resh **A**ir. Anaerobes are normal flora in GI tract, typically pathogenic elsewhere. Amin**O$_2$**glycosides are ineffective against anaerobes because these antibiotics require **O$_2$** to enter into bacterial cell.
Facultative anaerobes	Use fermentation and other nonoxygen-dependent pathways to generate ATP but are not killed by O$_2$.	Streptococci, staphylococci, and enteric gram ⊕ bacteria.

Intracellular bugs

Obligate intracellular	*Rickettsia*, *CHlamydia*, *COxiella*. Rely on host ATP.	Stay inside (cells) when it is Really CHilly and COld.
Facultative intracellular	*Salmonella*, *Neisseria*, *Brucella*, *Mycobacterium*, *Listeria*, *Francisella*, *Legionella*, *Yersinia pestis*.	Some Nasty Bugs May Live FacultativeLY.
Encapsulated bacteria 	Examples are *Pseudomonas aeruginosa*, *Streptococcus pneumoniae* A, *Haemophilus Influenzae* type B, *Neisseria meningitidis*, *Escherichia coli*, *Salmonella*, *Klebsiella pneumoniae*, and group B Strep. Their capsules serve as an antiphagocytic virulence factor. Capsular polysaccharide + protein conjugate serves as an antigen in vaccines.	Please SHINE my SKiS. Are opsonized, and then cleared by spleen. Asplenics have ↓ opsonizing ability and thus ↑ risk for severe infections. Give *S pneumoniae*, *H influenzae*, *N meningitidis* vaccines.
Encapsulated bacteria vaccines	Some vaccines containing polysaccharide capsule antigens are conjugated to a carrier protein, enhancing immunogenicity by promoting T-cell activation and subsequent class switching. A polysaccharide antigen alone cannot be presented to T cells.	Pneumococcal vaccine: PCV13 (pneumococcal conjugate vaccine), PPSV23 (pneumococcal polysaccharide vaccine with no conjugated protein) *H influenzae* type B (conjugate vaccine) Meningococcal vaccine (conjugate vaccine)
Urease-positive organisms	*Proteus*, *Cryptococcus*, *H pylori*, *Ureaplasma*, *Nocardia*, *Klebsiella*, *S epidermidis*, *S saprophyticus*. Urease hydrolyzes urea to release ammonia and CO_2 → ↑ pH. Predisposes to struvite (ammonium magnesium phosphate) stones, particularly *Proteus*.	Pee CHUNKSS.
Catalase-positive organisms 	Catalase degrades H_2O_2 into H_2O and bubbles of O_2 A before it can be converted to microbicidal products by the enzyme myeloperoxidase. People with chronic granulomatous disease (NADPH oxidase deficiency) have recurrent infections with certain catalase ⊕ organisms. Examples: *Nocardia*, *Pseudomonas*, *Listeria*, *Aspergillus*, *Candida*, *E coli*, Staphylococci, *Serratia*, *B cepacia*, *H pylori*.	Cats Need PLACESS to Belch their Hairballs.

Pigment-producing bacteria	*Actinomyces* ***israelii***—**yellow** "sulfur" **granules**, which are composed of filaments of bacteria.	**Israel** has **yellow sand**.
	S aureus—**yellow** pigment.	***Au**reus* (Latin) = **gold**.
	*P **aeru**ginosa*—blue-**green** pigment (pyocyanin and pyoverdin).	**Aeru**gula is **green**.
	*Serratia **marcescens***—**red** pigment.	*Serratia marcescens*—think **red maraschino** cherries.

In vivo biofilm-producing bacteria	*S epidermidis*	Catheter and prosthetic device infections
	Viridans streptococci (*S mutans*, *S sanguinis*)	Dental plaques, infective endocarditis
	P aeruginosa	Respiratory tree colonization in patients with cystic fibrosis, ventilator-associated pneumonia. Contact lens–associated keratitis
	Nontypeable (unencapsulated) *H influenzae*	Otitis media

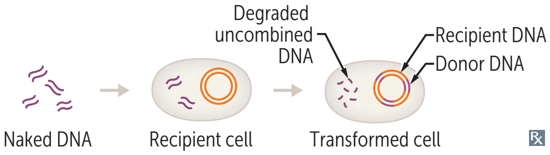
Bacterial virulence factors	These promote evasion of host immune response.
Protein A	Binds Fc region of IgG. Prevents opsonization and phagocytosis. Expressed by *S aureus*.
IgA protease	Enzyme that cleaves IgA, allowing bacteria to adhere to and colonize mucous membranes. Secreted by ***S** pneumoniae*, ***H** influenzae* type B, and ***N**eisseria* (**SHiN**).
M protein	Helps prevent phagocytosis. Expressed by group A streptococci. Shares similar epitopes to human cellular proteins (molecular mimicry); possibly underlies the autoimmune response seen in acute rheumatic fever.

Type III secretion system	Also known as "injectisome." Needle-like protein appendage facilitating direct delivery of toxins from certain gram ⊖ bacteria (eg, *Pseudomonas*, *Salmonella*, *Shigella*, *E coli*) to eukaryotic host cell.

Bacterial genetics

Transformation

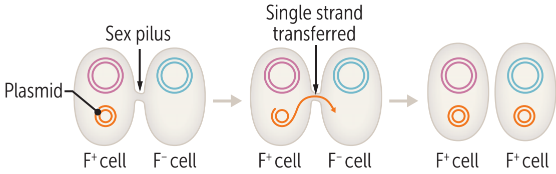
Competent bacteria are able to bind and import short pieces of environmental naked bacterial chromosomal DNA (from bacterial cell lysis). The transfer and expression of newly transferred genes is called transformation. A feature of many bacteria, especially ***S** pneumoniae*, ***H** influenzae* type B, and ***N**eisseria* (**SHiN**). Any DNA can be used. Adding deoxyribonuclease to environment will degrade naked DNA in medium → no transformation seen.


Degraded uncombined DNA
Recipient DNA
Donor DNA
Naked DNA
Recipient cell
Transformed cell

Conjugation

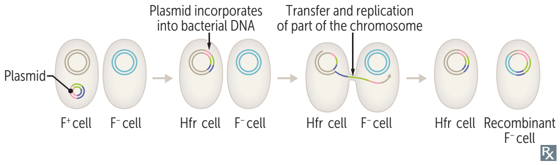
$F^+ \times F^-$

F^+ plasmid contains genes required for sex pilus and conjugation. Bacteria without this plasmid are termed F^-. Sex pilus on F^+ bacterium contacts F^- bacterium. A single strand of plasmid DNA is transferred across the conjugal bridge ("mating bridge"). No transfer of chromosomal DNA.


Sex pilus
Single strand transferred
Plasmid
F+ cell
F− cell
F+ cell
F− cell
F+ cell
F+ cell

$Hfr \times F^-$

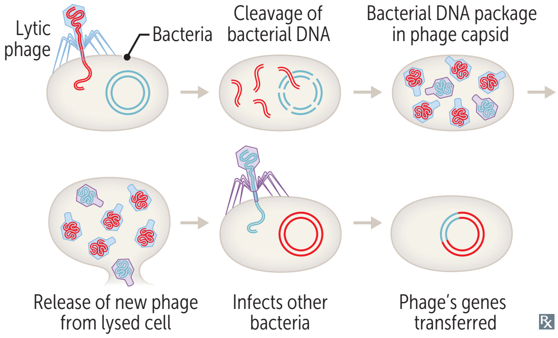
F^+ plasmid can become incorporated into bacterial chromosomal DNA, termed high-frequency recombination (Hfr) cell. Transfer of leading part of plasmid and a few flanking chromosomal genes. High-frequency recombination may integrate some of those bacterial genes. The recipient cell remains F^- but now may have new bacterial genes.


Plasmid incorporates into bacterial DNA
Transfer and replication of part of the chromosome
Plasmid
F+ cell
F− cell
Hfr cell
F− cell
Hfr cell
F− cell
Hfr cell
Recombinant F− cell

Transduction

Generalized

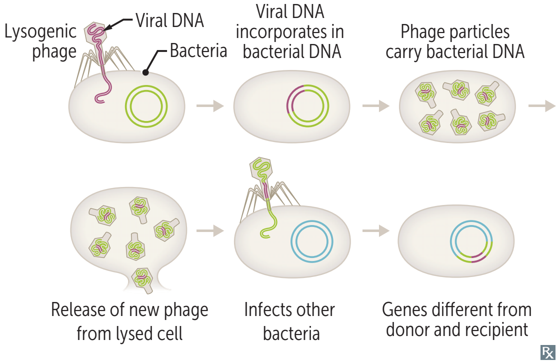
A "packaging" event. Lytic phage infects bacterium, leading to cleavage of bacterial DNA. Parts of bacterial chromosomal DNA may become packaged in phage capsid. Phage infects another bacterium, transferring these genes.


Lytic phage
Bacteria
Cleavage of bacterial DNA
Bacterial DNA package in phage capsid
Release of new phage from lysed cell
Infects other bacteria
Phage's genes transferred

Specialized

An "excision" event. Lysogenic phage infects bacterium; viral DNA incorporates into bacterial chromosome. When phage DNA is excised, flanking bacterial genes may be excised with it. DNA is packaged into phage capsid and can infect another bacterium.

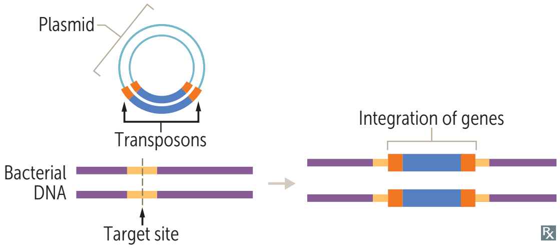
Genes for the following 5 bacterial toxins are encoded in a lysogenic phage (**ABCD'S**): Group **A** strep erythrogenic toxin, **B**otulinum toxin, **C**holera toxin, **D**iphtheria toxin, **S**higa toxin.


Lysogenic phage
Viral DNA
Bacteria
Viral DNA incorporates in bacterial DNA
Phage particles carry bacterial DNA
Release of new phage from lysed cell
Infects other bacteria
Genes different from donor and recipient

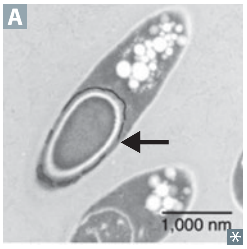
Bacterial genetics *(continued)*

Transposition

Segment of DNA (eg, transposon) that can "jump" (excision and reintegration) from one location to another, can transfer genes from plasmid to chromosome and vice versa. When excision occurs, may include some flanking chromosomal DNA, which can be incorporated into a plasmid and transferred to another bacterium (eg, *van*A gene from vancomycin-resistant *Enterococcus* to *S aureus*).



Spore-forming bacteria



Some bacteria can form spores **A** at the end of the stationary phase when nutrients are limited.

Spores are highly resistant to heat and chemicals. Have dipicolinic acid in their core. Have no metabolic activity. Must autoclave to potentially kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes.

Bacillus anthracis	Anthrax
Bacillus cereus	Food poisoning
Clostridium botulinum	Botulism
Clostridium difficile	Pseudomembranous colitis
Clostridium perfringens	Gas gangrene
Clostridium tetani	Tetanus

Main features of exotoxins and endotoxins

	Exotoxins	Endotoxin
SOURCE	Certain species of gram ⊕ and gram ⊖ bacteria	Outer cell membrane of most gram ⊖ bacteria
SECRETED FROM CELL	Yes	No
CHEMISTRY	Polypeptide	Lipid A component of LPS (structural part of bacteria; released when lysed)
LOCATION OF GENES	Plasmid or bacteriophage	Bacterial chromosome
ADVERSE EFFECTS	High (fatal dose on the order of 1 µg)	Low (fatal dose on the order of hundreds of micrograms)
CLINICAL EFFECTS	Various effects (see following pages)	Fever, shock (hypotension), DIC
MODE OF ACTION	Various modes (see following pages)	Induces TNF, IL-1, and IL-6
ANTIGENICITY	Induces high-titer antibodies called antitoxins	Poorly antigenic
VACCINES	Toxoids used as vaccines	No toxoids formed and no vaccine available
HEAT STABILITY	Destroyed rapidly at 60°C (except staphylococcal enterotoxin and *E coli* heat-stable toxin)	Stable at 100°C for 1 hr
TYPICAL DISEASES	Tetanus, botulism, diphtheria	Meningococcemia; sepsis by gram ⊖ rods

Bugs with exotoxins

BACTERIA	TOXIN	MECHANISM	MANIFESTATION
Inhibit protein synthesis			
Corynebacterium diphtheriae	Diphtheria toxin[a]	Inactivate elongation factor (EF-2)	Pharyngitis with pseudomembranes in throat and severe lymphadenopathy (bull neck)
Pseudomonas aeruginosa	Exotoxin A[a]		Host cell death
***Shigella* spp.**	Shiga toxin (ST)[a]	Inactivate 60S ribosome by removing adenine from rRNA	GI mucosal damage → dysentery; ST also enhances cytokine release, causing hemolytic-uremic syndrome (HUS)
Enterohemorrhagic *E coli* (EHEC)	Shiga-like toxin (SLT)[a]		SLT enhances cytokine release, causing HUS (prototypically in EHEC serotype O157:H7). Unlike *Shigella*, EHEC does not invade host cells
Increase fluid secretion			
Enterotoxigenic *E coli* (ETEC)	Heat-**labile** toxin (LT)[a]	Overactivates adenylate cyclase (↑ cAMP) → ↑ Cl^- secretion in gut and H_2O efflux	Watery diarrhea: "**labile** in the Air (Adenylate cyclase), **stable** on the Ground (Guanylate cyclase)"
	Heat-**stable** toxin (ST)	Overactivates guanylate cyclase (↑ cGMP) → ↓ resorption of NaCl and H_2O in gut	
Bacillus anthracis	Edema toxin[a]	Mimics the adenylate cyclase enzyme (↑ cAMP)	Likely responsible for characteristic edematous borders of black eschar in cutaneous anthrax
Vibrio cholerae	Cholera toxin[a]	Overactivates adenylate cyclase (↑ cAMP) by permanently activating G_s → ↑ Cl^- secretion in gut and H_2O efflux	Voluminous "rice-water" diarrhea
Inhibit phagocytic ability			
Bordetella pertussis	Pertussis toxin[a]	Overactivates adenylate cyclase (↑ cAMP) by disabling G_i, impairing phagocytosis to permit survival of microbe	Whooping cough—child coughs on expiration and "whoops" on inspiration (toxin may not actually be a cause of cough; can cause "100-day cough" in adults)
Inhibit release of neurotransmitter			
Clostridium tetani	Tetanospasmin[a]	Both are proteases that cleave SNARE (soluble NSF attachment protein receptor), a set of proteins required for neurotransmitter release via vesicular fusion	Spastic paralysis, risus sardonicus, and "lockjaw"; toxin prevents release of **inhibitory** (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord
Clostridium botulinum	Botulinum toxin[a]		Flaccid paralysis, floppy baby; toxin prevents release of **stimulatory** (ACh) signals at neuromuscular junctions → flaccid paralysis

[a] An AB toxin (aka, two-component toxin [or three for anthrax]) with B enabling binding and triggering uptake (endocytosis) of the active A component. The A components are usually ADP ribosyltransferases; others have enzymatic activities as listed in chart.

Bugs with exotoxins *(continued)*

BACTERIA	TOXIN	MECHANISM	MANIFESTATION
Lyse cell membranes			
Clostridium perfringens	Alpha toxin	Phospholipase (lecithinase) that degrades tissue and cell membranes	Degradation of phospholipids → myonecrosis (“gas gangrene”) and hemolysis (“double zone” of hemolysis on blood agar)
Streptococcus pyogenes	Streptolysin O	Protein that degrades cell membrane	Lyses RBCs; contributes to β-hemolysis; host antibodies against toxin (ASO) used to diagnose rheumatic fever (do not confuse with immune complexes of poststreptococcal glomerulonephritis)
Superantigens causing shock			
Staphylococcus aureus	Toxic shock syndrome toxin (TSST-1)	Binds to MHC II and TCR outside of antigen binding site to cause overwhelming release of IL-1, IL-2, IFN-γ, and TNF-α → shock	Toxic shock syndrome: fever, rash, shock; other toxins cause scalded skin syndrome (exfoliative toxin) and food poisoning (heat-stable enterotoxin)
Streptococcus pyogenes	Exotoxin A		Toxic shock–like syndrome: fever, rash, shock; scarlet fever

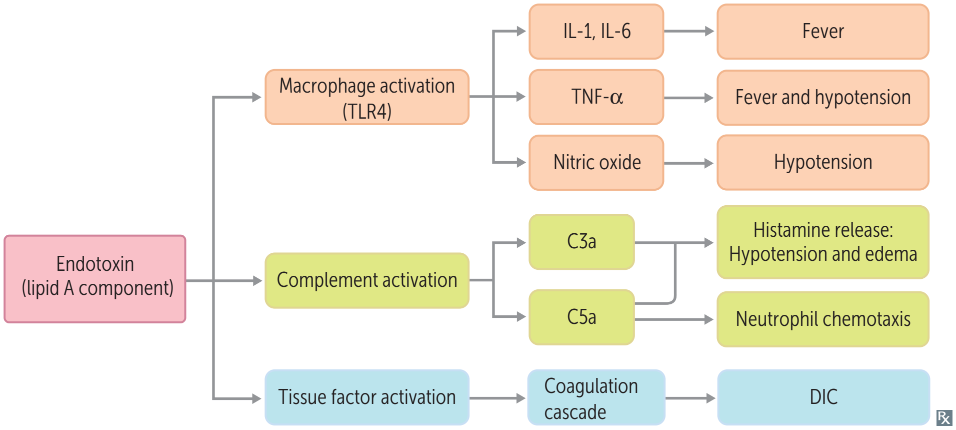
Endotoxin

LPS found in outer membrane of gram ⊖ bacteria (both cocci and rods). Composed of O antigen + core polysaccharide + lipid A (the toxic component).

Released upon cell lysis or by living cells by blebs detaching from outer surface membrane (vs exotoxin, which is actively secreted).

Three main effects: macrophage activation (TLR4), complement activation, and tissue factor activation.

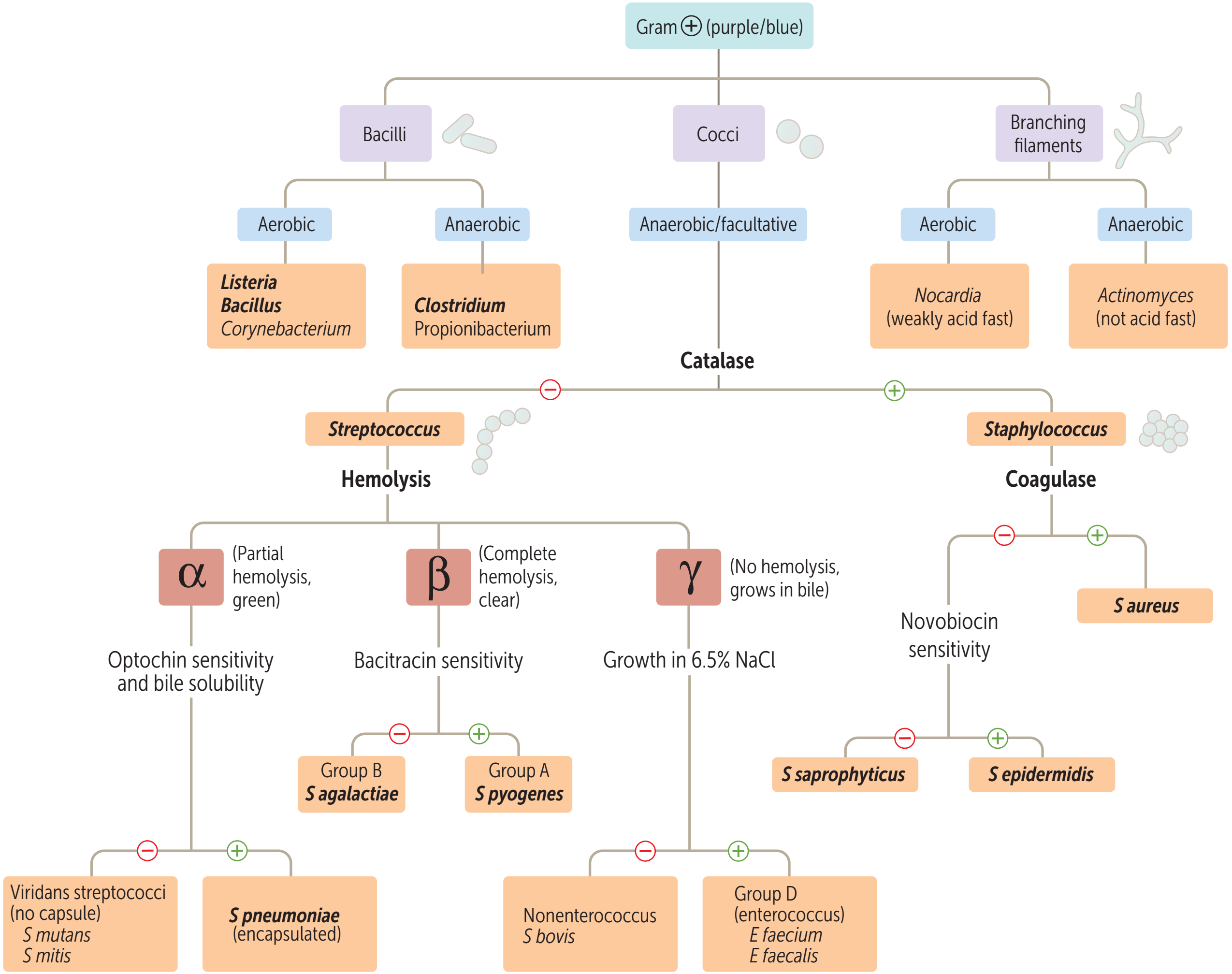
ENDOTOXINS:
- **E**dema
- **N**itric oxide
- **D**IC/**D**eath
- **O**uter membrane
- **T**NF-α
- **O**-antigen + core polysaccharide + lipid A
- e**X**tremely heat stable
- **I**L-1 and **I**L-6
- **N**eutrophil chemotaxis
- **S**hock



Endotoxin (lipid A component)
Macrophage activation (TLR4)
IL-1, IL-6
Fever
TNF-α
Fever and hypotension
Nitric oxide
Hypotension
Complement activation
C3a
Histamine release: Hypotension and edema
C5a
Neutrophil chemotaxis
Tissue factor activation
Coagulation cascade
DIC

▸ MICROBIOLOGY—CLINICAL BACTERIOLOGY

Gram-positive lab algorithm

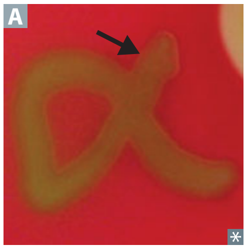

Gram ⊕ (purple/blue)
Bacilli
Cocci
Branching filaments
Aerobic
Anaerobic
Anaerobic/facultative
Aerobic
Anaerobic
Listeria
Bacillus
Corynebacterium
Clostridium
Propionibacterium
Nocardia (weakly acid fast)
Actinomyces (not acid fast)
Catalase
⊖
⊕
Streptococcus
Staphylococcus
Hemolysis
Coagulase
α (Partial hemolysis, green)
β (Complete hemolysis, clear)
γ (No hemolysis, grows in bile)
Optochin sensitivity and bile solubility
Bacitracin sensitivity
Growth in 6.5% NaCl
Novobiocin sensitivity
S aureus
⊖
⊕
Group B ***S agalactiae***
Group A ***S pyogenes***
S saprophyticus
S epidermidis
⊖
⊕
Viridans streptococci (no capsule) *S mutans* *S mitis*
S pneumoniae (encapsulated)
Nonenterococcus *S bovis*
Group D (enterococcus) *E faecium* *E faecalis*

Important **tests** are in **bold.** Important ***pathogens*** are in ***bold italics.***
Note: Enterococcus is either α- or γ-hemolytic.

Gram-positive cocci antibiotic tests

Staphylococci	**NO**vobiocin—***S****aprophyticus* is **R**esistant; ***E****pidermidis* is **S**ensitive.	On the office's "**staph**" retreat, there was **NO StRES**s.
Streptococci	**O**ptochin—***V****iridans* is **R**esistant; ***P****neumoniae* is **S**ensitive.	**OVRPS** (overpass).
	Bacitracin—group **B** strep are **R**esistant; group **A** strep are **S**ensitive.	**B-BRAS**.

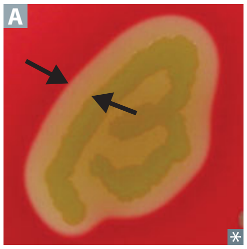
α-hemolytic bacteria



Gram ⊕ cocci. Partial reduction of hemoglobin causes greenish or brownish color without clearing around growth on blood agar A. Include the following organisms:

- *Streptococcus pneumoniae* (catalase ⊖ and optochin sensitive)
- Viridans streptococci (catalase ⊖ and optochin resistant)

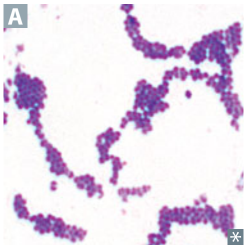
β-hemolytic bacteria



Gram ⊕ cocci. Complete lysis of RBCs → clear area surrounding colony on blood agar A. Include the following organisms:

- *Staphylococcus aureus* (catalase and coagulase ⊕)
- *Streptococcus pyogenes*—group A strep (catalase ⊖ and bacitracin sensitive)
- *Streptococcus agalactiae*—group B strep (catalase ⊖ and bacitracin resistant)

Staphylococcus aureus



Gram ⊕, β-hemolytic, catalase ⊕, coagulase ⊕ cocci in clusters A. Protein A (virulence factor) binds Fc-IgG, inhibiting complement activation and phagocytosis. Commonly colonizes the nares, axilla, and groin.

Causes:

- Inflammatory disease—skin infections, organ abscesses, pneumonia (often after influenza virus infection), endocarditis, septic arthritis, and osteomyelitis.
- Toxin-mediated disease—toxic shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins).
- MRSA (methicillin-resistant *S aureus*) infection—important cause of serious nosocomial and community-acquired infections; resistant to methicillin and nafcillin because of altered penicillin-binding protein.

TSST-1 is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation.

Staphylococcal toxic shock syndrome (TSS) presents as fever, vomiting, rash, desquamation, shock, end-organ failure. TSS results in ↑ AST, ↑ ALT, ↑ bilirubin. Associated with prolonged use of vaginal tampons or nasal packing.

Compare with *Streptococcus pyogenes* TSS (a toxic shock–like syndrome associated with painful skin infection).

S aureus food poisoning due to ingestion of preformed toxin → short incubation period (2–6 hr) followed by nonbloody diarrhea and emesis. Enterotoxin is heat stable → not destroyed by cooking.

Bad staph (*aureus*) make coagulase and toxins. Forms fibrin clot around self → abscess.

Staphylococcus epidermidis

Gram ⊕, catalase ⊕, coagulase ⊖, urease ⊕ cocci in clusters. Novobiocin sensitive. Does not ferment mannitol (vs *S aureus*).

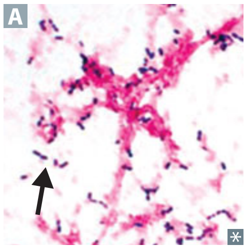
Normal flora of skin; contaminates blood cultures.

Infects prosthetic devices (eg, hip implant, heart valve) and IV catheters by producing adherent biofilms.

Staphylococcus saprophyticus

Gram ⊕, catalase ⊕, coagulase ⊖, urease ⊕ cocci in clusters. Novobiocin resistant.
Normal flora of female genital tract and perineum.
Second most common cause of uncomplicated UTI in young women (most common is *E coli*).

Streptococcus pneumoniae



Gram ⊕, lancet-shaped diplococci A. Encapsulated. IgA protease. Optochin sensitive. Most common cause of:

- Meningitis
- Otitis media (in children)
- Bacterial pneumonia
- Sinusitis

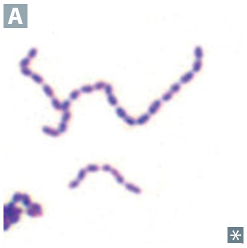
Pneumococcus is associated with “rusty” sputum, sepsis in patients with sickle cell disease, and asplenic patients.
No virulence without capsule.

Viridans group streptococci

Gram ⊕, α-hemolytic cocci. They are normal flora of the oropharynx that cause dental caries (*Streptococcus mutans* and *S mitis*) and subacute bacterial endocarditis at damaged **heart** valves (*S sanguinis*). Resistant to optochin, differentiating them from *S pneumoniae*, which is α-hemolytic but is optochin sensitive.

Sanguinis = **blood**. Think, “there is lots of **blood** in the **heart**” (endocarditis). *S sanguinis* makes dextrans, which bind to fibrin-platelet aggregates on damaged heart valves.
Viridans group strep live in the mouth because they are not afraid **of-the-chin** (**op-to-chin** resistant).

***Streptococcus pyogenes* (group A streptococci)**



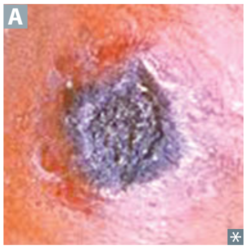
Gram ⊕ cocci in chains A. Group A strep cause:

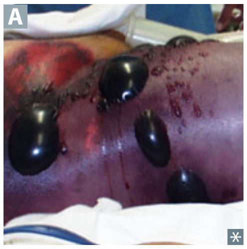
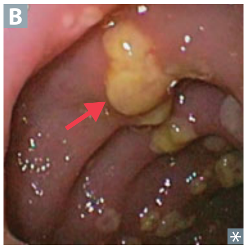
- Pyogenic—pharyngitis, cellulitis, impetigo (“honey-crusted” lesions), erysipelas
- Toxigenic—scarlet fever, toxic shock–like syndrome, necrotizing fasciitis
- Immunologic—rheumatic fever, glomerulonephritis

Bacitracin sensitive, β-hemolytic, pyrrolidonyl arylamidase (PYR) ⊕. Hyaluronic acid capsule inhibits phagocytosis. Antibodies to M protein enhance host defenses against *S pyogenes* but can give rise to rheumatic fever.
ASO titer or anti-DNase B antibodies indicate recent *S pyogenes* infection.

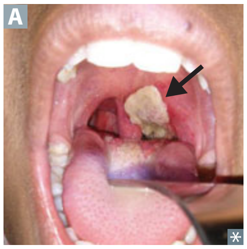
J♥NES (major criteria for acute rheumatic fever):
Joints—polyarthritis
♥—carditis
Nodules (subcutaneous)
Erythema marginatum
Sydenham chorea

Pharyngitis can result in rheumatic “**ph**ever” and glomerulone**ph**ritis.
Impetigo usually precedes glomerulonephritis.
Scarlet fever—blanching, sandpaper-like body rash, strawberry tongue, and circumoral pallor in the setting of group A streptococcal pharyngitis (erythrogenic toxin ⊕).

***Streptococcus agalactiae* (group B streptococci)**	Gram ⊕ cocci, bacitracin resistant, β-hemolytic, colonizes vagina; causes pneumonia, meningitis, and sepsis, mainly in babies. Produces CAMP factor, which enlarges the area of hemolysis formed by *S aureus*. (Note: CAMP stands for the authors of the test, not cyclic AMP.) Hippurate test ⊕. PYR ⊖. Screen pregnant women at 35–37 weeks of gestation with rectal + vaginal swabs. Patients with ⊕ culture receive intrapartum penicillin prophylaxis.	Group B for Babies!
Streptococcus bovis	Gram ⊕ cocci, colonizes the gut. *S gallolyticus* (*S bovis* biotype 1) can cause bacteremia and subacute endocarditis and is associated with colon cancer.	Bovis in the blood = cancer in the colon.
Enterococci	Gram ⊕ cocci. Enterococci (*E faecalis* and *E faecium*) are normal colonic flora that are penicillin G resistant and cause UTI, biliary tract infections, and subacute endocarditis (following GI/GU procedures). Catalase ⊖, PYR ⊕, variable hemolysis. VRE (vancomycin-resistant enterococci) are an important cause of nosocomial infection.	Enterococci, hardier than nonenterococcal group D, can grow in 6.5% NaCl and bile (lab test). *Entero* = intestine, *faecalis* = feces, *strepto* = twisted (chains), *coccus* = berry.
Bacillus anthracis	Gram ⊕, spore-forming rod that produces anthrax toxin. The only bacterium with a polypeptide capsule (contains D-glutamate). Colonies show a halo of projections, sometimes referred to as "medusa head" appearance.	
Cutaneous anthrax 	Painless papule surrounded by vesicles → ulcer with black eschar (A) (painless, necrotic) → uncommonly progresses to bacteremia and death.	
Pulmonary anthrax	Inhalation of spores → flu-like symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis, and shock. Also known as woolsorter's disease	

Bacillus cereus	Gram ⊕ rod. Causes food poisoning. Spores survive cooking rice. Keeping rice warm results in germination of spores and enterotoxin formation. Emetic type usually seen with rice and pasta. Nausea and vomiting within 1–5 hr. Caused by cereulide, a preformed toxin. Diarrheal type causes watery, nonbloody diarrhea and GI pain within 8–18 hr.	Reheated rice syndrome.
Clostridia (with exotoxins)	Gram ⊕, spore-forming, obligate anaerobic rods.	
C tetani	Produces tetano**spas**min, an exotoxin causing tetanus. Tetanus toxin (and botulinum toxin) are proteases that cleave SNARE proteins for neurotransmitters. Blocks release of inhibitory neurotransmitters, GABA and glycine, from Renshaw cells in spinal cord. Causes **spas**tic paralysis, trismus (lockjaw), risus sardonicus (raised eyebrows and open grin), opisthotonos (spasms of spinal extensors). Prevent with tetanus vaccine. Treat with antitoxin +/– vaccine booster, diazepam (for muscle spasms), and wound debridement.	**Tet**anus is **tet**anic paralysis.
C botulinum	Produces a heat-labile toxin that inhibits ACh release at the neuromuscular junction, causing botulism. In adults, disease is caused by ingestion of preformed toxin. In babies, ingestion of spores (eg, in honey) leads to disease (**floppy** baby syndrome). Treat with antitoxin.	Symptoms of botulism (the **4 D's**): **D**iplopia, **D**ysarthria, **D**ysphagia, **D**yspnea. ***Bot****ulinum* is from bad **bot**tles of food, juice, and honey (causes a descending **flaccid** paralysis). Local botox injections used to treat focal dystonia, achalasia, and muscle spasms. Also used for cosmetic reduction of facial wrinkles.
C perfringens 	Produces α toxin (lecithinase, a phospholipase) that can cause myonecrosis (gas gangrene A) and hemolysis. Spores can survive in undercooked food; when ingested, bacteria release heat-labile enterotoxin → food poisoning.	***Perf****ringens* **perf**orates a gangrenous leg.
C difficile 	Produces 2 toxins. Toxin A, an enterotoxin, binds to brush border of gut and alters fluid secretion. Toxin B, a cytotoxin, disrupts cytoskeleton via actin depolymerization. Both toxins lead to diarrhea → pseudomembranous colitis B. Often 2° to antibiotic use, especially clindamycin or ampicillin; associated with PPI use. Diagnosed by detecting one or both toxins in stool by antigen detection or PCR.	***Di****fficile* causes **di**arrhea. Treatment: metronidazole or oral vancomycin. For recurrent cases, consider repeating prior regimen, fidaxomicin, or fecal microbiota transplant.

Corynebacterium diphtheriae



Gram ⊕ rod; transmitted via respiratory droplets. Causes diphtheria via exotoxin encoded by β-prophage. Potent exotoxin inhibits protein synthesis via ADP-ribosylation of EF-2.

Symptoms include pseudomembranous pharyngitis (grayish-white membrane A) with lymphadenopathy, myocarditis, and arrhythmias.

Lab diagnosis based on gram ⊕ rods with metachromatic (blue and red) granules and ⊕ Elek test for toxin.

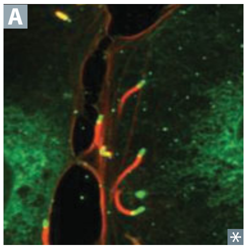
Toxoid vaccine prevents diphtheria.

Coryne = club shaped.

Black colonies on cystine-tellurite agar.

ABCDEFG:
- **A**DP-ribosylation
- **β**-prophage
- ***C****orynebacterium*
- ***D****iphtheriae*
- **E**longation **F**actor 2
- **G**ranules

Listeria monocytogenes



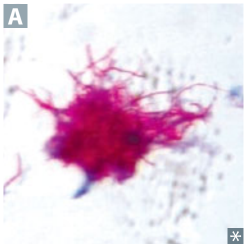
Gram ⊕, facultative intracellular rod; acquired by ingestion of unpasteurized dairy products and cold deli meats, via transplacental transmission, or by vaginal transmission during birth. Grows well at refrigeration temperatures (4°–10°C; "cold enrichment").

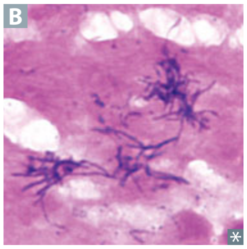
Forms "rocket tails" (red in A) via actin polymerization that allow intracellular movement and cell-to-cell spread across cell membranes, thereby avoiding antibody. Characteristic tumbling motility in broth.

Can cause amnionitis, septicemia, and spontaneous abortion in pregnant women; granulomatosis infantiseptica; neonatal meningitis; meningitis in immunocompromised patients; mild, self-limited gastroenteritis in healthy individuals.

Treatment: ampicillin.

Nocardia vs *Actinomyces*



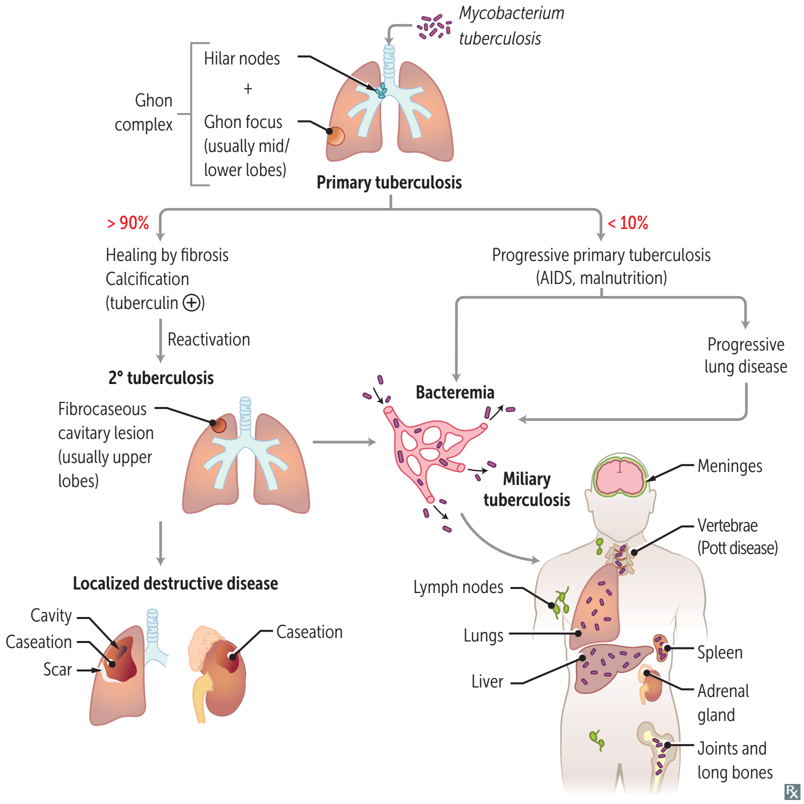


Both are gram ⊕ and form long, branching filaments resembling fungi.

Nocardia	*Actinomyces*
Aerobe	Anaerobe
Acid fast (weak) A	Not acid fast B
Found in soil	Normal oral, reproductive, and GI flora
Causes pulmonary infections in immunocompromised (can mimic TB but with ⊖ PPD); cutaneous infections after trauma in immunocompetent; can spread to CNS	Causes oral/facial abscesses that drain through sinus tracts; often associated with dental caries/extraction; forms yellow "sulfur granules"; can also cause PID with IUDs
Treat with sulfonamides (TMP-SMX)	Treat with penicillin

Treatment is a **SNAP**: **S**ulfonamides—***N****ocardia*; ***A****ctinomyces*—**P**enicillin

Primary and secondary tuberculosis

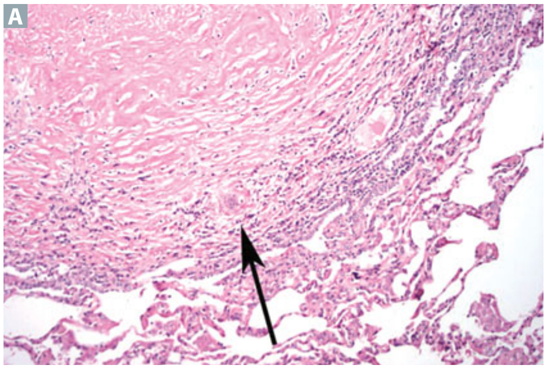

Mycobacterium tuberculosis
Ghon complex
Hilar nodes
+
Ghon focus (usually mid/lower lobes)
Primary tuberculosis
> 90%
< 10%
Healing by fibrosis
Calcification
(tuberculin ⊕)
Progressive primary tuberculosis (AIDS, malnutrition)
Reactivation
Progressive lung disease
2° tuberculosis
Bacteremia
Fibrocaseous cavitary lesion (usually upper lobes)
Miliary tuberculosis
Meninges
Vertebrae (Pott disease)
Localized destructive disease
Lymph nodes
Cavity
Caseation
Scar
Caseation
Lungs
Spleen
Liver
Adrenal gland
Joints and long bones

PPD ⊕ if current infection or past exposure.

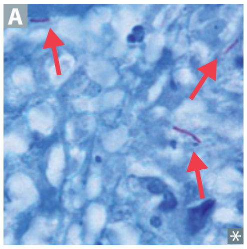
PPD ⊖ if no infection and in sarcoidosis or HIV infection (especially with low CD4+ cell count).

Interferon-γ release assay (IGRA) has fewer false positives from BCG vaccination.

Caseating granulomas **A** with central necrosis (upper left) and Langhans giant cells (arrow) are characteristic of 2° tuberculosis.



Mycobacteria



Mycobacterium tuberculosis (TB, often resistant to multiple drugs).

M avium–intracellulare (causes disseminated, non-TB disease in AIDS; often resistant to multiple drugs). Prophylaxis with azithromycin when CD4+ count < 50 cells/mm^3.

M scrofulaceum (cervical lymphadenitis in children).

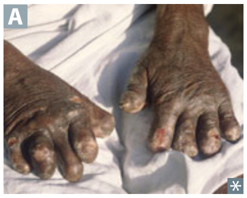
M marinum (hand infection in aquarium handlers).

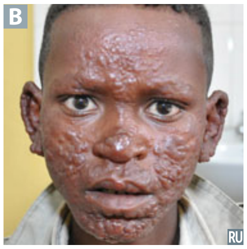
All mycobacteria are acid-fast organisms (pink rods; arrows in **A**).

TB symptoms include fever, night sweats, weight loss, cough (nonproductive or productive), hemoptysis.

Cord factor creates a "serpentine cord" appearance in virulent *M tuberculosis* strains; activates macrophages (promoting granuloma formation) and induces release of TNF-α. Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

Leprosy (Hansen disease)





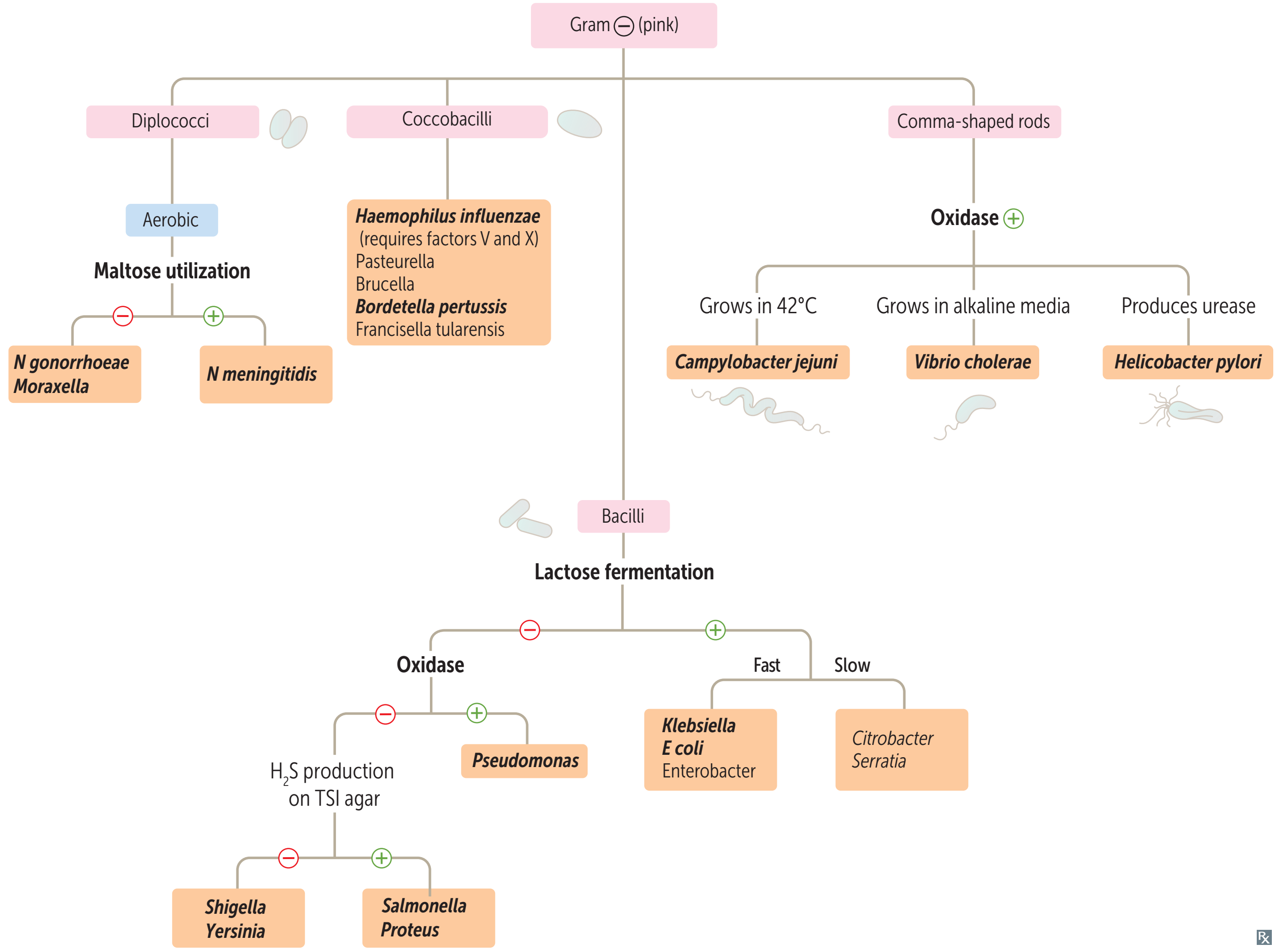
Caused by *Mycobacterium leprae*, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves—"glove and stocking" loss of sensation **A**) and cannot be grown in vitro. Diagnosed via skin biopsy or tissue PCR. Reservoir in United States: armadillos.

Hansen disease has 2 forms (many cases fall temporarily between two extremes):

- Lepromatous—presents diffusely over the skin, with leonine (lion-like) facies **B**, and is communicable; characterized by low cell-mediated immunity with a humoral Th2 response. Lepromatous form can be lethal.
- Tuberculoid—limited to a few hypoesthetic, hairless skin plaques; characterized by high cell-mediated immunity with a largely Th1-type immune response.

Treatment: dapsone and rifampin for tuberculoid form; clofazimine is added for lepromatous form.

Gram-negative lab algorithm


Gram ⊖ (pink)
Diplococci
Aerobic
Maltose utilization
⊖
⊕
N gonorrhoeae
Moraxella
N meningitidis
Coccobacilli
Haemophilus influenzae
(requires factors V and X)
Pasteurella
Brucella
Bordetella pertussis
Francisella tularensis
Comma-shaped rods
Oxidase ⊕
Grows in 42°C
Grows in alkaline media
Produces urease
Campylobacter jejuni
Vibrio cholerae
Helicobacter pylori
Bacilli
Lactose fermentation
⊖
⊕
Oxidase
⊖
⊕
Pseudomonas
H_2S production on TSI agar
⊖
⊕
Shigella
Yersinia
Salmonella
Proteus
Fast
Slow
Klebsiella
E coli
Enterobacter
Citrobacter
Serratia

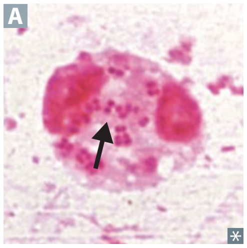
Important **tests** are in **bold.** Important ***pathogens*** are in ***bold italics.***

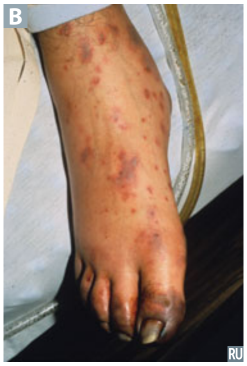
Lactose-fermenting enteric bacteria

Fermentation of lactose → pink colonies on MacConkey agar. Examples include *Klebsiella*, *E coli*, *Enterobacter*, and *Serratia* (weak fermenter). *E coli* produces β-galactosidase, which breaks down lactose into glucose and galactose.

Lactose is key.
Test with MacConKEE'S agar.
EMB agar—lactose fermenters grow as purple/black colonies. *E coli* grows colonies with a green sheen.

Neisseria



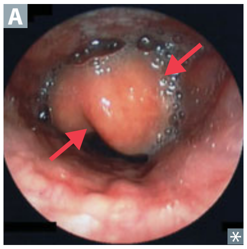


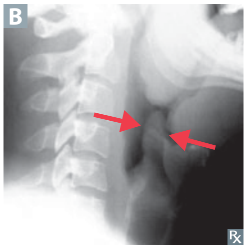
Gram ⊖ diplococci. Metabolize glucose and produce IgA proteases. Contain lipooligosaccharides (LOS) with strong endotoxin activity. *N gonorrhoeae* is often intracellular (within neutrophils) A.

MeninGococci ferment Maltose and Glucose.
Gonococci ferment Glucose.

Gonococci	Meningococci
No polysaccharide capsule	Polysaccharide capsule
No maltose metabolized	Maltose fermentation
No vaccine due to antigenic variation of pilus proteins	Vaccine (type B vaccine not widely available)
Sexually or perinatally transmitted	Transmitted via respiratory and oral secretions
Causes gonorrhea, septic arthritis, neonatal conjunctivitis (2–5 days after birth), pelvic inflammatory disease (PID), and Fitz-Hugh–Curtis syndrome	Causes meningococcemia with petechial hemorrhages and gangrene of toes B, meningitis, Waterhouse-Friderichsen syndrome (adrenal insufficiency, fever, DIC, shock)
Condoms ↓ sexual transmission, erythromycin eye ointment prevents neonatal blindness	Rifampin, ciprofloxacin, or ceftriaxone prophylaxis in close contacts
Treatment: ceftriaxone + (azithromycin or doxycycline) for possible chlamydial coinfection	Treatment: ceftriaxone or penicillin G

Haemophilus influenzae





Small gram ⊖ (coccobacillary) rod. Aerosol transmission. Nontypeable (unencapsulated) strains are the most common cause of mucosal infections (otitis media, conjunctivitis, bronchitis) as well as invasive infections since the vaccine for capsular type b was introduced. Produces IgA protease. Culture on chocolate agar, which contains factors V (NAD^+) and X (hematin) for growth; can also be grown with *S aureus*, which provides factor V through the hemolysis of RBCs. *HaEMOPhilus* causes Epiglottitis (endoscopic appearance in A, can be "cherry red" in children; "thumb sign" on x-ray B), Meningitis, Otitis media, and Pneumonia.
Treatment: amoxicillin +/– clavulanate for mucosal infections; ceftriaxone for meningitis; rifampin prophylaxis for close contacts.

Vaccine contains type b capsular polysaccharide (polyribosylribitol phosphate) conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age.
Does not cause the flu (influenza virus does).

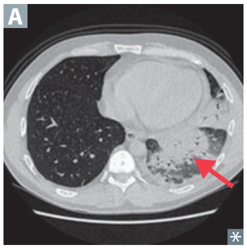
Bordetella pertussis

Gram ⊖, aerobic coccobacillus. Virulence factors include pertussis toxin (disables G_i) and tracheal cytotoxin. Three clinical stages:

- Catarrhal—low-grade fevers, coryza.
- Paroxysmal—paroxysms of intense cough followed by inspiratory "whoop" ("whooping cough"), posttussive vomiting.
- Convalescent—gradual recovery of chronic cough.

Prevented by Tdap, DTaP vaccines. May be mistaken as viral infection due to lymphocytic infiltrate resulting from immune response.

Legionella pneumophila



Gram ⊖ rod. Gram stains poorly—use **silver** stain. Grow on **charcoal** yeast extract medium with **iron** and **cysteine**. Detected by presence of antigen in urine. Labs may show hyponatremia. Aerosol transmission from environmental water source habitat (eg, air conditioning systems, hot water tanks). No person-to-person transmission.

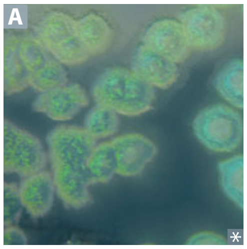
Treatment: macrolide or quinolone.

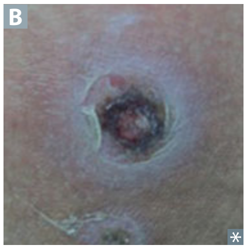
Legionnaires' disease—severe pneumonia (often unilateral and lobar A), fever, GI and CNS symptoms. Common in smokers and in chronic lung disease.

Pontiac fever—mild flu-like syndrome.

Think of a French **legionnaire** (soldier) with his **silver** helmet, sitting around a campfire (**charcoal**) with his **iron** dagger—he is no **sissy** (cysteine).

Pseudomonas aeruginosa





Aerobic, motile, gram ⊖ rod. Non-lactose fermenting, oxidase ⊕. Produces pyocyanin (blue-green pigment A); has a grape-like odor. Produces endotoxin (fever, shock), exotoxin A (inactivates EF-2), phospholipase C (degrades cell membranes), and pyocyanin (generates reactive oxygen species).

PSEUDOMONAS is associated with:

- **P**neumonia, pyocyanin
- **S**epsis
- **E**cthyma gangrenosum
- **U**TIs
- **D**iabetes, drug use
- **O**steomyelitis (eg, puncture wounds)
- **M**ucoid polysaccharide capsule
- **O**titis externa (swimmer's ear)
- **N**osocomial infections (catheters, equipment)
- Exotoxin **A**
- **S**kin infections (hot tub folliculitis)

Treatments include "**CAMPFIRE**" drugs:

- **C**arbapenems
- **A**minoglycosides
- **M**onobactams
- **P**olymyxins (eg, polymyxin B, colistin)
- **F**luoroquinolones (eg, ciprofloxacin, levofloxacin)
- Th**IR**d- and fourth-generation cephalosporins (eg, ceftazidime, cefepime)
- **E**xtended-spectrum penicillins (eg, piperacillin, ticarcillin)

Aeruginosa—**aer**obic.

Mucoid polysaccharide capsule may contribute to chronic pneumonia in cystic fibrosis patients due to biofilm formation.

Can cause wound infection in burn victims.

Corneal ulcers/keratitis in contact lens wearers/minor eye trauma.

Frequently found in water → hot tub folliculitis.

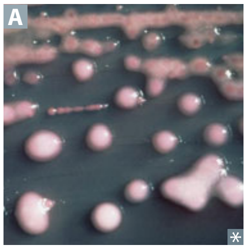
Ecthyma gangrenosum—rapidly progressive, necrotic cutaneous lesion B caused by *Pseudomonas* bacteremia. Typically seen in immunocompromised patients.

Escherichia coli

Gram ⊖ rod. *E coli* virulence factors: fimbriae—cystitis and pyelonephritis (P-pili); K capsule—pneumonia, neonatal meningitis; LPS endotoxin—septic shock.

STRAIN	TOXIN AND MECHANISM	PRESENTATION
EIEC	Microbe invades intestinal mucosa and causes necrosis and inflammation.	**I**nvasive; dysentery. Clinical manifestations similar to *Shigella*.
ETEC	Produces heat-labile and heat-stable entero**T**oxins. No inflammation or invasion.	**T**ravelers' diarrhea (watery).
EPEC	No toxin produced. Adheres to apical surface, flattens villi, prevents absorption.	Diarrhea, usually in children (**P**ediatrics).
EHEC	O157:H7 is most common serotype in US. Often transmitted via undercooked meat, raw leafy vegetables. Shiga-like toxin causes **hemolytic-uremic syndrome**: triad of anemia, thrombocytopenia, and acute renal failure due to microthrombi forming on damaged endothelium → mechanical hemolysis (with schistocytes on peripheral blood smear), platelet consumption, and ↓ renal blood flow.	Dysentery (toxin alone causes necrosis and inflammation). Does not ferment sorbitol (vs other *E coli*). **H**emorrhagic, **H**amburgers, **H**emolytic-uremic syndrome.

Klebsiella

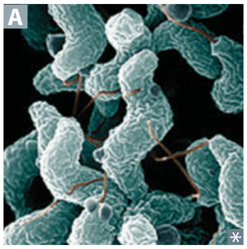


Gram ⊖ rod; intestinal flora that causes lobar pneumonia in alcoholics and diabetics when aspirated. Very mucoid colonies A caused by abundant polysaccharide capsules. Dark red "currant jelly" sputum (blood/mucus).

Also cause of nosocomial UTIs.

5 A's of *Klebsiell***A**:
- **A**spiration pneumonia
- **A**bscess in lungs and liver
- **A**lcoholics
- Di-**A**-betics
- "Curr-**A**-nt jelly" sputum

Campylobacter jejuni



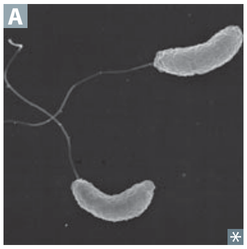
Gram ⊖, comma or S shaped (with polar flagella) A, oxidase ⊕, grows at **42°C** ("*Campylobacter* likes the **hot campfire**"). Major cause of bloody diarrhea, especially in children. Fecal-oral transmission through person-to-person contact or via ingestion of undercooked contaminated poultry or meat, unpasteurized milk. Contact with infected animals (dogs, cats, pigs) is also a risk factor. Common antecedent to Guillain-Barré syndrome and reactive arthritis.

Salmonella vs *Shigella*

Both *Salmonella* and *Shigella* are gram ⊖ rods, non-lactose fermenters, oxidase ⊖, and can invade the GI tract via M cells of Peyer patches.

	***Salmon**ella typhi*	***Salmon**ella* spp. (except *S typhi*)	*Shigella*
RESERVOIRS	Humans only	Humans and animals	Humans only
SPREAD	Can disseminate hematogenously	Can disseminate hematogenously	Cell to cell; no hematogenous spread
H_2S PRODUCTION	Yes	Yes	No
FLAGELLA	Yes (**salmon swim**)	Yes (**salmon swim**)	No
VIRULENCE FACTORS	Endotoxin; Vi capsule	Endotoxin	Endotoxin; Shiga toxin (enterotoxin)
INFECTIOUS DOSE (ID_{50})	High—large inoculum required because organism inactivated by gastric acids	High	Low—very small inoculum required; resistant to gastric acids
EFFECT OF ANTIBIOTICS ON FECAL EXCRETION	Prolongs duration	Prolongs duration	Shortens duration
IMMUNE RESPONSE	Primarily monocytes	PMNs in disseminated disease	Primarily PMN infiltration
GI MANIFESTATIONS	Constipation, followed by diarrhea	Diarrhea (possibly bloody)	Bloody diarrhea (bacillary dysentery)
VACCINE	Oral vaccine contains live attenuated *S typhi* IM vaccine contains Vi capsular polysaccharide	No vaccine	No vaccine
UNIQUE PROPERTIES	▪ Causes typhoid fever (rose spots on abdomen, constipation, abdominal pain, fever); treat with ceftriaxone or fluoroquinolone ▪ Carrier state with gallbladder colonization	▪ Poultry, eggs, pets, and turtles are common sources ▪ Antibiotics not indicated ▪ Gastroenteritis is usually caused by non-typhoidal *Salmonella*	▪ **Four F's**: **F**ingers, **F**lies, **F**ood, **F**eces ▪ In order of decreasing severity (less toxin produced): *S dysenteriae*, *S flexneri*, *S boydii*, *S sonnei* ▪ Invasion of M cells is key to pathogenicity: organisms that produce little toxin can cause disease

Vibrio cholerae

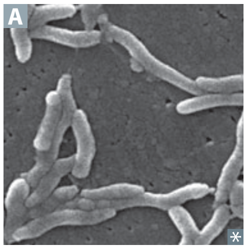


Gram ⊖, flagellated, comma shaped A, oxidase ⊕, grows in alkaline media. Endemic to developing countries. Produces profuse rice-water diarrhea via enterotoxin that permanently activates G_s, ↑ cAMP. Sensitive to stomach acid (acid labile); requires large inoculum (high ID_{50}) unless host has ↓ gastric acidity. Transmitted via ingestion of contaminated water or uncooked food (eg, raw shellfish). Prompt oral rehydration is necessary.

Yersinia enterocolitica

Gram ⊖ rod. Usually transmitted from pet feces (eg, puppies), contaminated milk, or pork. Causes acute diarrhea or pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis).

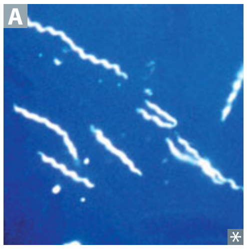
Helicobacter pylori



Curved, flagellated (motile), gram ⊖ rod A that is **triple** ⊕: catalase ⊕, oxidase ⊕, and urease ⊕ (can use urea breath test or fecal antigen test for diagnosis). Urease produces ammonia, creating an alkaline environment, which helps *H pylori* survive in acidic mucosa. Colonizes mainly antrum of stomach; causes gastritis and peptic ulcers (especially duodenal). Risk factor for peptic ulcer disease, gastric adenocarcinoma, and MALT lymphoma.

Most common initial treatment is **triple** therapy: Amoxicillin (metronidazole if penicillin allergy) + Clarithromycin + Proton pump inhibitor; Antibiotics Cure *Pylori*.

Spirochetes



Spiral-shaped bacteria A with axial filaments. Includes *Borrelia* (big size), *Leptospira*, and *Treponema*. Only *Borrelia* can be visualized using aniline dyes (Wright or Giemsa stain) in light microscopy due to size. *Treponema* is visualized by dark-field microscopy or direct fluorescent antibody (DFA) microscopy.

BLT.
Borrelia is Big.

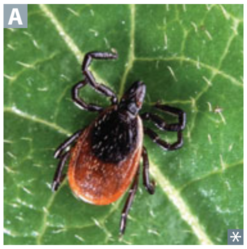
Leptospira interrogans

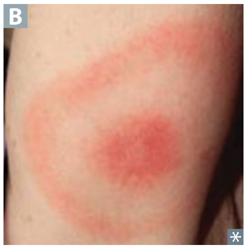
Spirochete with hook-shaped ends found in water contaminated with animal urine.

Leptospirosis—flu-like symptoms, myalgias (classically of calves), jaundice, photophobia with conjunctival suffusion (erythema without exudate). Prevalent among surfers and in tropics (eg, Hawaii).

Weil disease (icterohemorrhagic leptospirosis)—severe form with jaundice and azotemia from liver and kidney dysfunction, fever, hemorrhage, and anemia.

Lyme disease





Caused by *Borrelia burgdorferi*, which is transmitted by the *Ixodes* deer tick A (also vector for *Anaplasma* spp. and protozoa *Babesia*). Natural reservoir is the mouse (and important to tick life cycle).

Common in northeastern United States.

Stage 1—early localized: erythema migrans (typical "bulls-eye" configuration B is pathognomonic but not always present), flu-like symptoms.

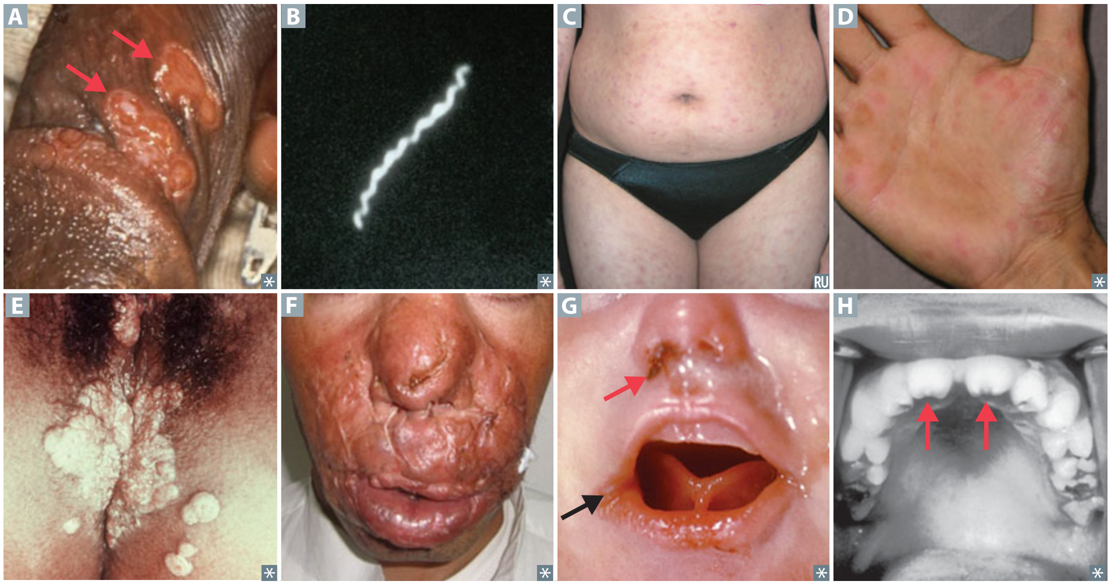
Stage 2—early disseminated: secondary lesions, carditis, AV block, facial nerve (Bell) palsy, migratory myalgias/transient arthritis.

Stage 3—late disseminated: encephalopathies, chronic arthritis.

A Key Lyme pie to the FACE:
- Facial nerve palsy (typically bilateral)
- Arthritis
- Cardiac block
- Erythema migrans

Treatment: doxycycline (1st line); amoxicillin and cefuroxime in pregnant women and children.

Syphilis	Caused by spirochete *Treponema pallidum*.
Primary syphilis	Localized disease presenting with **painless** chancre A. If available, use dark-field microscopy to visualize treponemes in fluid from chancre B. VDRL ⊕ in ~ 80%.
Secondary syphilis	Disseminated disease with constitutional symptoms, maculopapular rash C (including palms D and soles), condylomata lata E (smooth, moist, painless, wart-like white lesions on genitals), lymphadenopathy, patchy hair loss; also confirmable with dark-field microscopy. Serologic testing: VDRL/RPR (nonspecific), confirm diagnosis with specific test (eg, FTA-ABS). Secondary syphilis = Systemic. Latent syphilis (⊕ serology without symptoms) may follow.
Tertiary syphilis	Gummas F (chronic granulomas), aortitis (vasa vasorum destruction), neurosyphilis (tabes dorsalis, "general paresis"), Argyll Robertson pupil (constricts with accommodation but is not reactive to light; also called "prostitute's pupil" since it accommodates but does not react). Signs: broad-based ataxia, ⊕ Romberg, Charcot joint, stroke without hypertension. For neurosyphilis: test spinal fluid with VDRL, FTA-ABS, and PCR.
Congenital syphilis	Presents with facial abnormalities such as rhagades (linear scars at angle of mouth, black arrow in G), snuffles (nasal discharge, red arrow in G), saddle nose, notched (Hutchinson) teeth H, mulberry molars, and short maxilla; saber shins; CN VIII deafness. To prevent, treat mother early in pregnancy, as placental transmission typically occurs after first trimester.



VDRL false positives	VDRL detects nonspecific antibody that reacts with beef cardiolipin. Quantitative, inexpensive, and widely available test for syphilis (sensitive but not specific).	False-positive results on VDRL with: Viral infection (eg, EBV, hepatitis) Drugs Rheumatic fever Lupus and leprosy

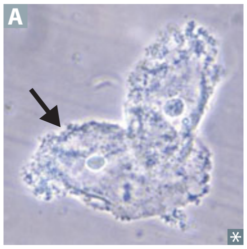
Jarisch-Herxheimer reaction	Flu-like syndrome (fever, chills, headache, myalgia) after antibiotics are started; due to killed bacteria (usually spirochetes) releasing toxins.

Zoonotic bacteria

Zoonosis: infectious disease transmitted between animals and humans.

SPECIES	DISEASE	TRANSMISSION AND SOURCE
***Anaplasma* spp.**	Anaplasmosis	*Ixodes* ticks (live on deer and mice)
***Bartonella* spp.**	Cat scratch disease, bacillary angiomatosis	Cat scratch
Borrelia burgdorferi	Lyme disease	*Ixodes* ticks (live on deer and mice)
Borrelia recurrentis	Relapsing fever	Louse (recurrent due to variable surface antigens)
***Brucella* spp.**	Brucellosis/undulant fever	Unpasteurized dairy
Campylobacter	Bloody diarrhea	Feces from infected pets/animals; contaminated meats/foods/hands
Chlamydophila psittaci	Psittacosis	Parrots, other birds
Coxiella burnetii	Q fever	Aerosols of cattle/sheep amniotic fluid
Ehrlichia chaffeensis	Ehrlichiosis	*Amblyomma* (Lone Star tick)
Francisella tularensis	Tularemia	Ticks, rabbits, deer flies
***Leptospira* spp.**	Leptospirosis	Animal urine in water; recreational water use
Mycobacterium leprae	Leprosy	Humans with lepromatous leprosy; armadillo (rare)
Pasteurella multocida	Cellulitis, osteomyelitis	Animal bite, cats, dogs
Rickettsia prowazekii	Epidemic typhus	Human to human via human body louse
Rickettsia rickettsii	Rocky Mountain spotted fever	*Dermacentor* (dog tick)
Rickettsia typhi	Endemic typhus	Fleas
***Salmonella* spp. (except *S typhi*)**	Diarrhea (which may be bloody), vomiting, fever, abdominal cramps	Reptiles and poultry
Yersinia pestis	Plague	Fleas (rats and prairie dogs are reservoirs)

Gardnerella vaginalis



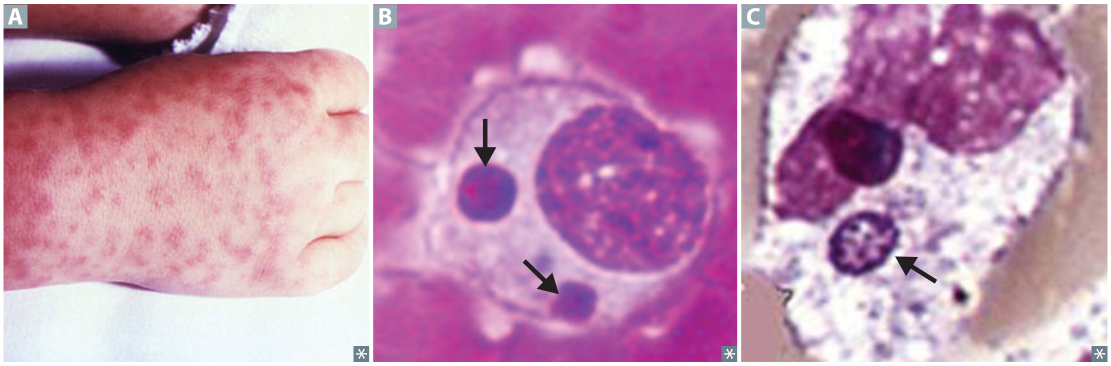
A pleomorphic, gram-variable rod involved in bacterial vaginosis. Presents as a gray vaginal discharge with a fishy smell; nonpainful (vs vaginitis). Associated with sexual activity, but not sexually transmitted. Bacterial vaginosis is also characterized by overgrowth of certain anaerobic bacteria in vagina. Clue cells (vaginal epithelial cells covered with *Gardnerella*) have stippled appearance along outer margin (arrow in A).

Treatment: metronidazole or clindamycin.

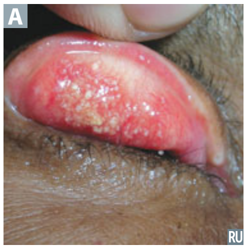
I don't have a clue why I smell fish in the vagina garden!

Amine whiff test—mixing discharge with 10% KOH enhances fishy odor.

Rickettsial diseases and vector-borne illnesses	Treatment: doxycycline (caution during pregnancy; alternative is chloramphenicol).	
RASH COMMON		
Rocky Mountain spotted fever	*Rickettsia rickettsii*, vector is tick. Despite its name, disease occurs primarily in the South Atlantic states, especially North Carolina. Rash typically starts at wrists A and ankles and then spreads to trunk, palms, and soles.	Classic triad—headache, fever, rash (vasculitis). Palms and soles rash is seen in Coxsackievirus A infection (hand, foot, and mouth disease), Rocky Mountain spotted fever, and 2° Syphilis (you drive CARS using your palms and soles).
Typhus	Endemic (fleas)—*R typhi*. Epidemic (human body louse)—*R prowazekii*. Rash starts centrally and spreads out, sparing palms and soles.	*Rickettsii* on the wRists, Typhus on the Trunk.
RASH RARE		
Ehrlichiosis	*Ehrlichia*, vector is tick. Monocytes with morulae B (mulberry-like inclusions) in cytoplasm.	MEGA berry— Monocytes = Ehrlichiosis Granulocytes = Anaplasmosis
Anaplasmosis	*Anaplasma*, vector is tick. Granulocytes with morulae C in cytoplasm.	
Q fever	*Coxiella burnetii*, no arthropod vector. Spores inhaled as aerosols from cattle/sheep amniotic fluid. Presents as pneumonia. Common cause of culture ⊖ endocarditis.	Q fever is Queer because it has no rash or vector and its causative organism can survive outside in its endospore form. Not in the *Rickettsia* genus, but closely related.



Chlamydiae



Chlamydiae cannot make their own ATP. They are obligate intracellular organisms that cause mucosal infections. 2 forms:

- Elementary body (small, dense) is "Enfectious" and Enters cell via Endocytosis; transforms into reticulate body.
- Reticulate body Replicates in cell by fission; Reorganizes into elementary bodies.

Chlamydia trachomatis causes reactive arthritis (Reiter syndrome), follicular conjunctivitis A, nongonococcal urethritis, and PID.

Chlamydophila pneumoniae and *Chlamydophila psittaci* cause atypical pneumonia; transmitted by aerosol.

Treatment: azithromycin (favored because one-time treatment) or doxycycline (+ ceftriaxone for possible concomitant gonorrhea).

Chlamys = cloak (intracellular).

C psittaci—has an avian reservoir (parrots), causes atypical pneumonia.

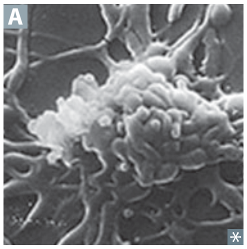
Lab diagnosis: PCR, nucleic acid amplification test. Cytoplasmic inclusions (reticulate bodies) seen on Giemsa or fluorescent antibody–stained smear.

The chlamydial cell wall lacks classic peptidoglycan (due to reduced muramic acid), rendering β-lactam antibiotics ineffective.

Chlamydia trachomatis serotypes

Types A, B, and C	Chronic infection, cause blindness due to follicular conjunctivitis in Africa.	ABC = Africa, Blindness, Chronic infection.
Types D–K	Urethritis/PID, ectopic pregnancy, neonatal pneumonia (staccato cough) with eosinophilia, neonatal conjunctivitis (1–2 weeks after birth).	D–K = everything else. Neonatal disease can be acquired during passage through infected birth canal.
Types L1, L2, and L3	Lymphogranuloma venereum—small, painless ulcers on genitals → swollen, painful inguinal lymph nodes that ulcerate (buboes). Treat with doxycycline.	

Mycoplasma pneumoniae



Classic cause of atypical "walking" pneumonia (insidious onset, headache, nonproductive cough, patchy or diffuse interstitial infiltrate). X-ray looks worse than patient. High titer of cold agglutinins (IgM), which can agglutinate or lyse RBCs. Grown on Eaton agar.

Treatment: macrolides, doxycycline, or fluoroquinolone (penicillin ineffective since *Mycoplasma* have no cell wall).

No cell wall. Not seen on Gram stain. Pleomorphic A.

Bacterial membrane contains sterols for stability.

Mycoplasmal pneumonia is more common in patients < 30 years old.

Frequent outbreaks in military recruits and prisons.

Mycoplasma gets cold without a coat (cell wall).

▶ MICROBIOLOGY—MYCOLOGY

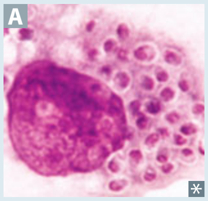
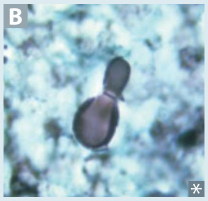
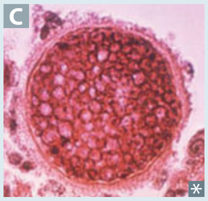
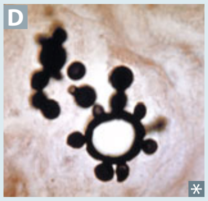
Systemic mycoses

All of the following can cause pneumonia and can disseminate.

All are caused by dimorphic fungi: cold (20°C) = mold; heat (37°C) = yeast. Only exception is *Coccidioides*, which is a spherule (not yeast) in tissue.

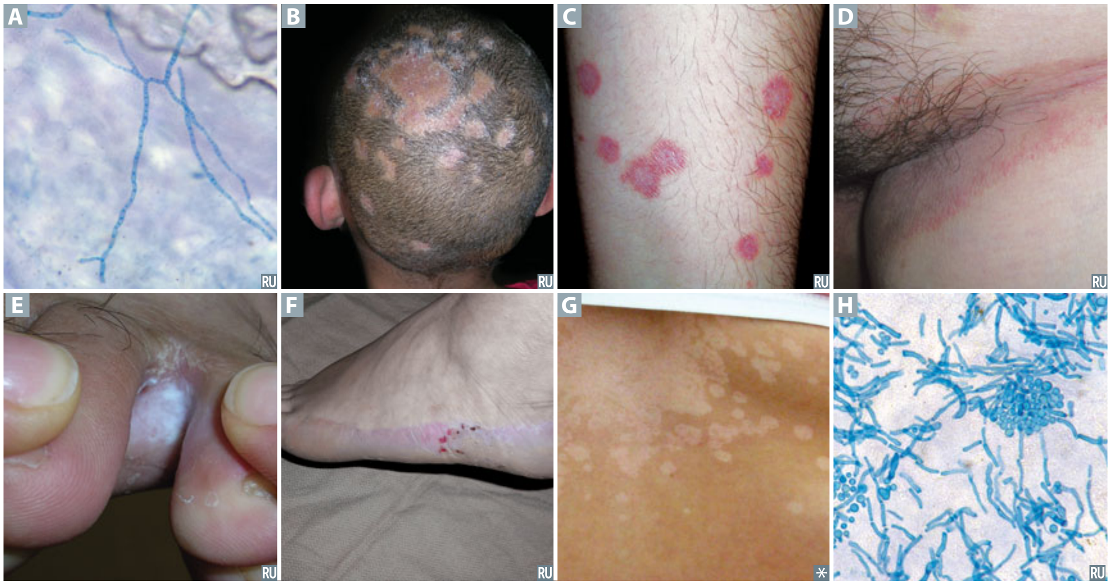
Systemic mycoses can form granulomas (like TB); cannot be transmitted person-to-person (unlike TB).

Treatment: fluconazole or itraconazole for **local** infection; amphotericin B for **systemic** infection.

DISEASE	ENDEMIC LOCATION	PATHOLOGIC FEATURES	UNIQUE SIGNS/SYMPTOMS	NOTES
Histoplasmosis 	Mississippi and Ohio River Valleys	Macrophage filled with *Histoplasma* (smaller than RBC) A	Palatal/tongue ulcers, splenomegaly	Histo hides (within macrophages) Bird (eg, starlings) or bat droppings Diagnosis via urine/serum antigen
Blastomycosis 	Eastern and Central US	Broad-based budding of *Blastomyces* (same size as RBC) B	Inflammatory lung disease, can disseminate to skin/bone Verrucous skin lesions can simulate SCC Forms granulomatous nodules	Blasto buds broadly
Coccidioidomycosis 	Southwestern US, California	Spherule (much larger than RBC) filled with endospores of *Coccidioides* C	Disseminates to skin/bone Erythema nodosum (desert bumps) or multiforme Arthralgias (desert rheumatism) Can cause meningitis	
Paracoccidioidomycosis 	Latin America	Budding yeast of *Paracoccidioides* with "captain's wheel" formation (much larger than RBC) D	Similar to Coccidioidomycosis, males > females	Paracoccidio parasails with the captain's wheel all the way to Latin America

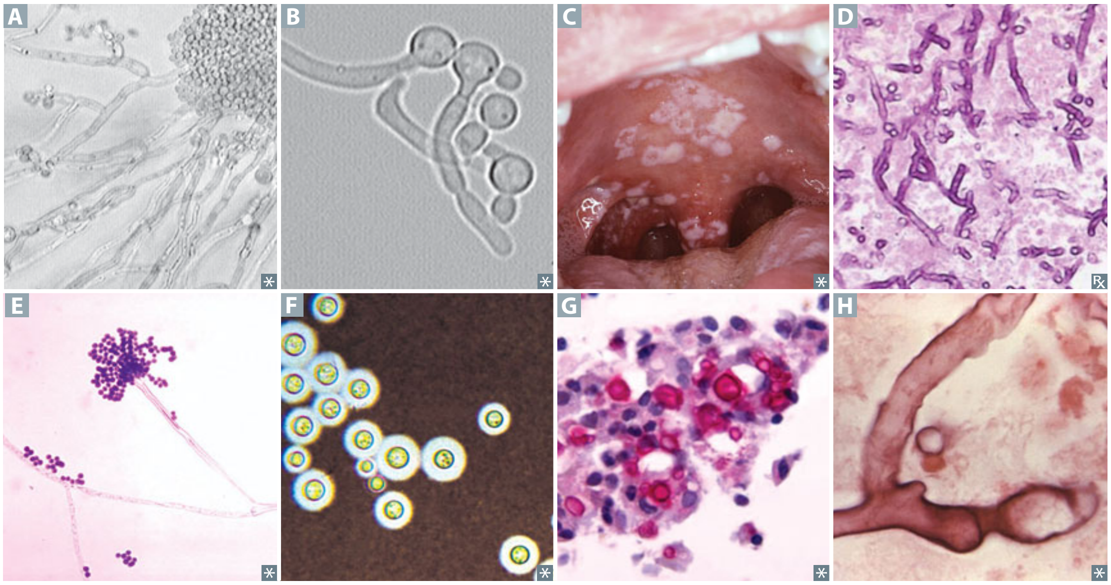
Cutaneous mycoses

Tinea (dermatophytes)	Tinea is the clinical name given to dermatophyte (cutaneous fungal) infections. Dermatophytes include *Microsporum*, *Trichophyton*, and *Epidermophyton*. Branching septate hyphae visible on KOH preparation with blue fungal stain A. Associated with pruritus.
Tinea capitis	Occurs on head, scalp. Associated with lymphadenopathy, alopecia, scaling B.
Tinea corporis	Occurs on torso. Characterized by erythematous scaling rings (“ringworm”) and central clearing C. Can be acquired from contact with an infected cat or dog.
Tinea cruris	Occurs in inguinal area D. Often does not show the central clearing seen in tinea corporis.
Tinea pedis	Three varieties: ▪ Interdigital E; most common ▪ Moccasin distribution F ▪ Vesicular type
Tinea unguium	Onychomycosis; occurs on nails.
Tinea (pityriasis) versicolor	Caused by *Malassezia* spp. (*Pityrosporum* spp.), a yeast-like fungus (not a dermatophyte despite being called tinea). Degradation of lipids produces acids that damage melanocytes and cause hypopigmented G, hyperpigmented, and/or pink patches. Less pruritic than dermatophytes. Can occur any time of year, but more common in summer (hot, humid weather). “Spaghetti and meatballs” appearance on microscopy H. Treatment: selenium sulfide, topical and/or oral antifungal medications.



Opportunistic fungal infections

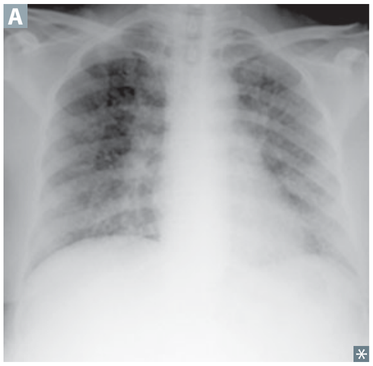
Candida albicans	*alba* = white. Dimorphic; forms pseudohyphae and budding yeasts at 20°C A, germ tubes at 37°C B. Systemic or superficial fungal infection. Causes oral C and esophageal thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (diabetes, use of antibiotics), diaper rash, endocarditis (IV drug users), disseminated candidiasis (especially in neutropenic patients), chronic mucocutaneous candidiasis. Treatment: oral fluconazole/topical azole for vaginal; nystatin, fluconazole, or caspofungin for oral/esophageal; fluconazole, caspofungin, or amphotericin B for systemic.
Aspergillus fumigatus	Septate hyphae that branch at 45° **A**cute **A**ngle D. Produces conidia in radiating chains at end of conidiophore E. Causes invasive aspergillosis in immunocompromised, patients with chronic granulomatous disease. Can cause aspergillomas in pre-existing lung cavities, especially after TB infection. Some species of *Aspergillus* produce **A**flatoxins (associated with hepatocellular carcinoma). **Allergic bronchopulmonary aspergillosis** (ABPA): hypersensitivity response associated with asthma and cystic fibrosis; may cause bronchiectasis and eosinophilia.
Cryptococcus neoformans	5–10 μm with narrow budding. Heavily encapsulated yeast. Not dimorphic. Found in soil, pigeon droppings. Acquired through inhalation with hematogenous dissemination to meninges. Culture on Sabouraud agar. Highlighted with India ink (clear halo F) and mucicarmine (red inner capsule G). Latex agglutination test detects polysaccharide capsular antigen and is more specific. Causes cryptococcosis, cryptococcal meningitis, cryptococcal encephalitis (“soap bubble” lesions in brain), primarily in immunocompromised. Treatment: amphotericin B + flucytosine followed by fluconazole for cryptococcal meningitis.
***Mucor* and *Rhizopus* spp.**	Irregular, broad, nonseptate hyphae branching at wide angles H. Mucormycosis. Causes disease mostly in ketoacidotic diabetic and/or neutropenic patients (eg, leukemia). Fungi proliferate in blood vessel walls, penetrate cribriform plate, and enter brain. Rhinocerebral, frontal lobe abscess; cavernous sinus thrombosis. Headache, facial pain, black necrotic eschar on face; may have cranial nerve involvement. Treatment: surgical debridement, amphotericin B.

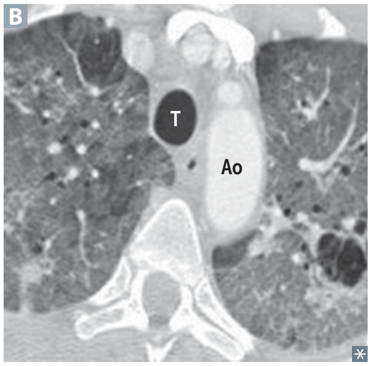


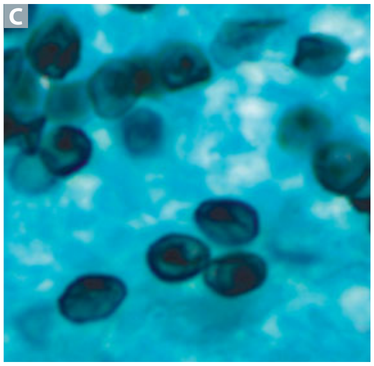
Pneumocystis jirovecii

Causes *Pneumocystis* pneumonia (PCP), a diffuse interstitial pneumonia A. Yeast-like fungus (originally classified as protozoan). Inhaled. Most infections are asymptomatic. Immunosuppression (eg, AIDS) predisposes to disease. Diffuse, bilateral ground-glass opacities on CXR/CT B. Diagnosed by lung biopsy or lavage. Disc-shaped yeast seen on methenamine silver stain of lung tissue C.

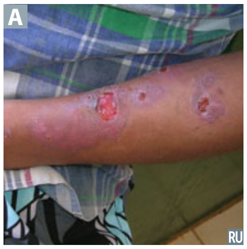
Treatment/prophylaxis: TMP-SMX, pentamidine, dapsone (prophylaxis only), atovaquone. Start prophylaxis when CD4+ count drops to < 200 cells/mm^3 in HIV patients.







Sporothrix schenckii



Sporotrichosis. Dimorphic, **cigar**-shaped budding yeast that grows in branching hyphae with **rose**ttes of conidia; lives on vegetation. When spores are traumatically introduced into the skin, typically by a thorn ("**rose gardener**'s disease"), causes local pustule or ulcer A with nodules along draining lymphatics (ascending lymphangitis). Disseminated disease possible in immunocompromised host.

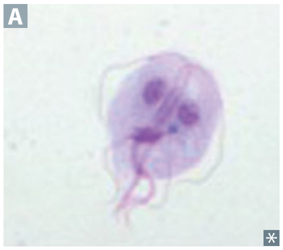
Treatment: itraconazole or **pot**assium iodide.

Think of a **rose gardener** who smokes a **cigar** and **pot**.

▸ MICROBIOLOGY—PARASITOLOGY

Protozoa—gastrointestinal infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Giardia lamblia	**Giardiasis**—bloating, flatulence, foul-smelling, fatty diarrhea (often seen in campers/hikers)—think **fat**-rich **Ghirardelli** chocolates for **fatty** stools of ***Giardia***	Cysts in water	Multinucleated trophozoites A or cysts B in stool, antigen detection	Metronidazole
Entamoeba histolytica	**Amebiasis**—bloody diarrhea (dysentery), liver abscess (“anchovy paste” exudate), RUQ pain; histology shows flask-shaped ulcer	Cysts in water	Serology and/or trophozoites (with engulfed RBCs C in the cytoplasm) or cysts with up to 4 nuclei in stool D; **E**ntamoeba **E**ats **E**rythrocytes, antigen detection	Metronidazole; paromomycin or iodoquinol for asymptomatic cyst passers
Cryptosporidium	Severe diarrhea in AIDS Mild disease (watery diarrhea) in immunocompetent hosts	Oocysts in water	Oocysts on acid-fast stain E, antigen detection	Prevention (by filtering city water supplies); nitazoxanide in immunocompetent hosts

A


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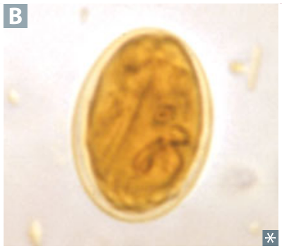

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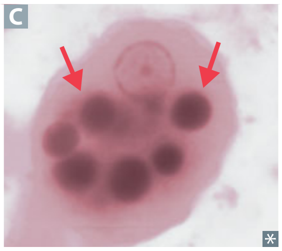

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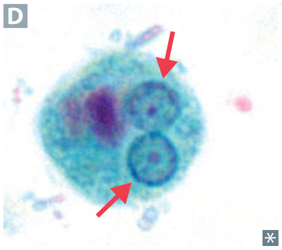

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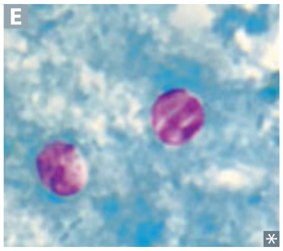
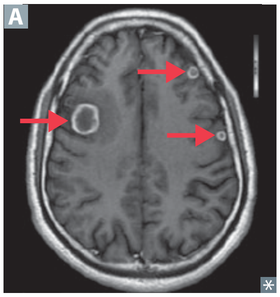
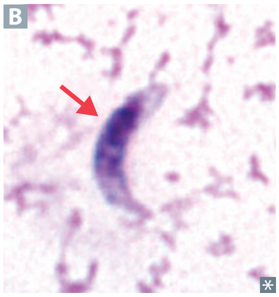
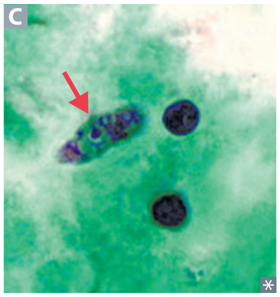


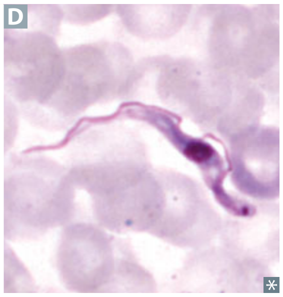
Protozoa—CNS infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Toxoplasma gondii	Congenital toxoplasmosis = classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications; reactivation in AIDS → brain abscesses usually seen as multiple ring-enhancing lesions on MRI A	Cysts in meat (most common); oocysts in cat feces; crosses placenta (pregnant women should avoid cats)	Serology, biopsy (tachyzoite) B	Sulfadiazine + pyrimethamine
Naegleria fowleri	Rapidly fatal meningoencephalitis	Swimming in **freshwater** lakes (think **Nalgene** bottle filled with **fresh water** containing ***Naegleria***); enters via cribriform plate	Amoebas in spinal fluid C	Amphotericin B has been effective for a few survivors
Trypanosoma brucei	**African sleeping sickness**—enlarged lymph nodes, recurring fever (due to antigenic variation), somnolence, coma Two subspecies: *Trypanosoma brucei rhodesiense*, *Trypanosoma brucei gambiense*	Tsetse fly, a painful bite	Trypomastigote in blood smear D	**Sur**amin for blood-borne disease or **mel**arsoprol for CNS penetration (“I **sur**e am **mel**low when I’m **sleeping**”; remember **mel**atonin helps with **sleep**)

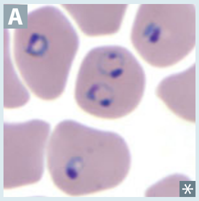
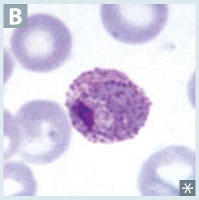
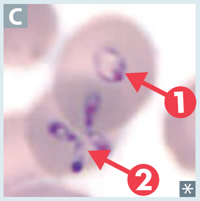




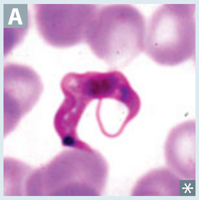
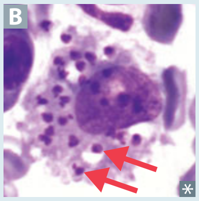
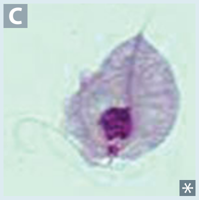




Protozoa—hematologic infections

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Plasmodium ***P vivax/ovale*** ***P falciparum*** ***P malariae***  	**Malaria**—fever, headache, anemia, splenomegaly *P vivax/ovale*—48-hr cycle (tertian; includes fever on first day and third day, thus fevers are actually 48 hr apart); dormant form (hypnozoite) in liver *P falciparum*—severe; irregular fever patterns; parasitized RBCs occlude capillaries in brain (cerebral malaria), kidneys, lungs *P malariae*—72-hr cycle (quartan)	*Anopheles* mosquito	Blood smear: trophozoite ring form within RBC **A**, schizont containing merozoites; red granules (Schüffner stippling) **B** throughout RBC cytoplasm seen with *P vivax/ovale*	Chloroquine (for sensitive species), which blocks *Plasmodium* heme polymerase; if resistant, use mefloquine or atovaquone/proguanil If life-threatening, use intravenous quinidine or artesunate (test for G6PD deficiency) For *P vivax/ovale*, add primaquine for hypnozoite (test for G6PD deficiency)
Babesia 	**Babesiosis**—fever and hemolytic anemia; predominantly in northeastern United States; asplenia ↑ risk of severe disease	*Ixodes* tick (same as *Borrelia burgdorferi* of Lyme disease; may often coinfect humans)	Blood smear: ring form **C1**, "Maltese cross" **C2**; PCR	Atovaquone + azithromycin

Protozoa—others

ORGANISM	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
Visceral infections				
Trypanosoma cruzi 	**Chagas disease**—dilated cardiomyopathy with apical atrophy, megacolon, megaesophagus; predominantly in South America Unilateral periorbital swelling (Romaña sign) characteristic of acute stage	Reduviid bug ("kissing bug") feces, deposited in a painless bite (much like a kiss)	Trypomastigote in blood smear A	Benznidazole or nifurtimox; Cruzing in my Benz, with a fur coat on
Leishmania donovani 	**Visceral leishmaniasis (kala-azar)**—spiking fevers, hepatosplenomegaly, pancytopenia **Cutaneous leishmaniasis**—skin ulcers	Sandfly	Macrophages containing amastigotes B	Amphotericin B, sodium stibogluconate
Sexually transmitted infections				
Trichomonas vaginalis 	**Vaginitis**—foul-smelling, greenish discharge; itching and burning; do not confuse with *Gardnerella vaginalis*, a gram-variable bacterium associated with bacterial vaginosis	Sexual (cannot exist outside human because it cannot form cysts)	Trophozoites (motile) C on wet mount; "strawberry cervix"	Metronidazole for patient and partner (prophylaxis)

Nematode routes of infection

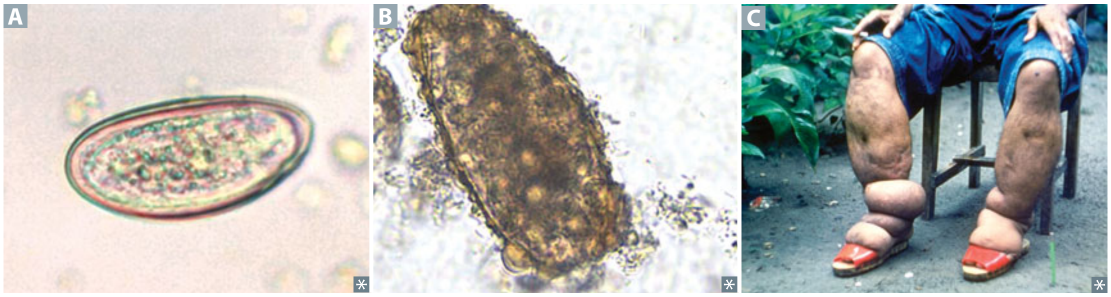
Ingested—*Enterobius*, *Ascaris*, *Toxocara*, *Trichinella*	You'll get sick if you EATT these!
Cutaneous—*Strongyloides*, *Ancylostoma*, *Necator*	These get into your feet from the SANd.
Bites—*Loa loa*, *Onchocerca volvulus*, *Wuchereria bancrofti*	Lay LOW to avoid getting bitten.

Immune response to helminths

Eosinophils act by type I and type II hypersensitivity reactions in responding to helminths. Type I—neutralization of histamine and leukotrienes. Type II—eosinophils attach to surface of helminths via IgE and release cytotoxins (eg, major basic protein) contained in their granules.

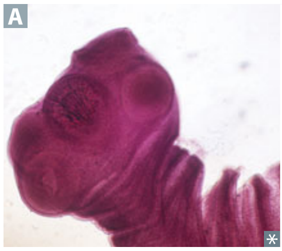
Nematodes (roundworms)

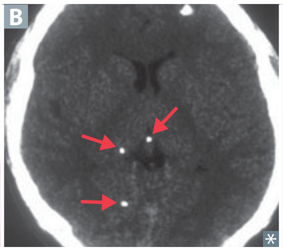
ORGANISM	DISEASE	TRANSMISSION	TREATMENT
Intestinal			
***Enterobius vermicularis* (pinworm)**	Causes anal pruritus (diagnosed by seeing egg A via the tape test)	Fecal-oral	Pyrantel pamoate or **bend**azoles (because worms are **bend**y)
***Ascaris lumbricoides* (giant roundworm)**	May cause obstruction at ileocecal valve, biliary obstruction, intestinal perforation, migrates from nose/mouth	Fecal-oral; knobby-coated, oval eggs seen in feces under microscope B	Bendazoles
***Strongyloides stercoralis* (threadworm)**	Causes vomiting, diarrhea, epigastric pain (may mimic peptic ulcer)	Larvae in soil penetrate skin; rhabditiform larvae seen in feces under microscope	Ivermectin or bendazoles
***Ancylostoma duodenale, Necator americanus* (hookworms)**	Cause anemia by sucking blood from intestinal wall **Cutaneous larva migrans**—pruritic, serpiginous rash from walking barefoot on contaminated beach	Larvae penetrate skin	Bendazoles or pyrantel pamoate
Trichinella spiralis	Larvae enter bloodstream, encyst in striated muscle → muscle inflammation **Trichinosis**—fever, vomiting, nausea, periorbital edema, myalgia	Undercooked meat (especially pork); fecal-oral (less likely)	Bendazoles
***Trichuris trichiura* (whipworm)**	Often asymptomatic; loose stools/anemia, rectal prolapse in children (heavy infection)	Fecal-oral	Bendazoles
Tissue			
Toxocara canis	**Visceral larva migrans**—nematodes migrate to blood through intestinal wall → inflammation and damage. Often affects heart (myocarditis), liver, eyes (visual impairment, blindness), and CNS (seizures, coma)	Fecal-oral	Bendazoles
Onchocerca volvulus	Skin changes, loss of elastic fibers, and river blindness (**black** flies, **black** skin nodules, "**black** sight"); allergic reaction to microfilaria possible	Female blackfly	Ivermectin (**iver**mectin for **river** blindness)
Loa loa	Swelling in skin, worm in conjunctiva	Deer fly, horse fly, mango fly	Diethylcarbamazine
Wuchereria bancrofti	**Lymphatic filariasis (elephantiasis)**—worms invade lymph nodes → inflammation → lymphedema C; symptom onset after 9 mo–1 yr	Female mosquito	Diethylcarbamazine

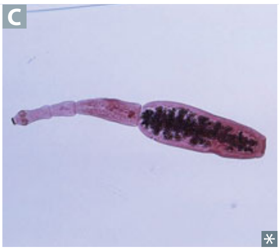


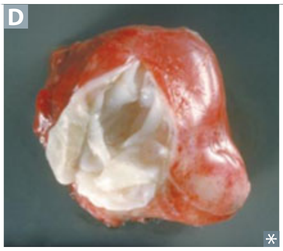
Cestodes (tapeworms)

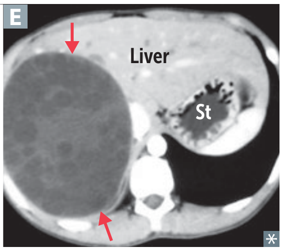
ORGANISM	DISEASE	TRANSMISSION	TREATMENT
Taenia solium **A**	Intestinal tapeworm	Ingestion of larvae encysted in undercooked pork	Praziquantel
	Cysticercosis, neurocysticercosis **B**	Ingestion of eggs in food contaminated with human feces	Praziquantel; albendazole for neurocysticercosis
Diphyllobothrium latum	Vitamin B_{12} deficiency (tapeworm competes for B_{12} in intestine) → megaloblastic anemia	Ingestion of larvae in raw freshwater fish	Praziquantel
Echinococcus granulosus **C**	Hydatid cysts (“eggshell calcification” **D**) in liver **E**; cyst rupture can cause anaphylaxis	Ingestion of eggs in food contaminated with dog feces Sheep are an intermediate host	Albendazole



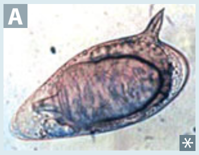
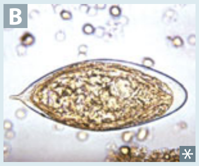




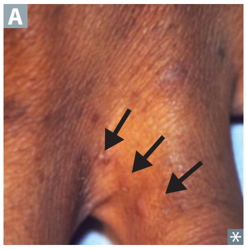
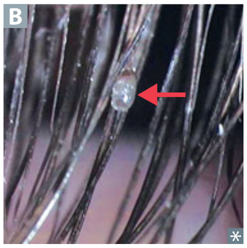




Trematodes (flukes)

ORGANISM	DISEASE	TRANSMISSION	TREATMENT
Schistosoma  	Liver and spleen enlargement (*S mansoni*, egg with lateral spine **A**), fibrosis, inflammation, portal hypertension Chronic infection with *S haematobium* (egg with terminal spine **B**) can lead to squamous cell carcinoma of the bladder (painless hematuria) and pulmonary hypertension	Snails are host; cercariae penetrate skin of humans	Praziquantel
Clonorchis sinensis	Biliary tract inflammation → pigmented gallstones Associated with cholangiocarcinoma	Undercooked fish	Praziquantel

Ectoparasites

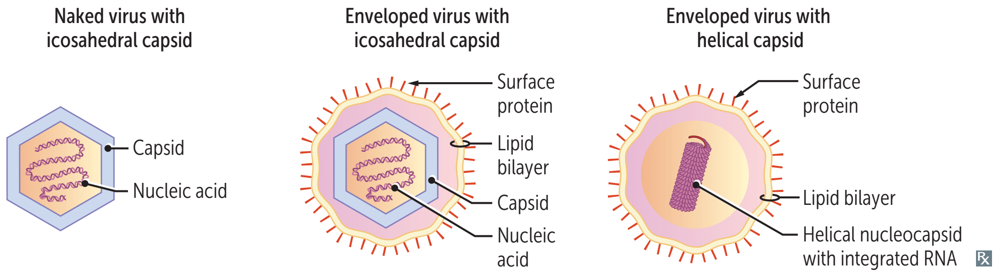
Sarcoptes scabiei  	Mite burrow into stratum corneum and cause **scabies**—pruritus (worse at night) and serpiginous burrows (lines) in webspace of hands and feet A.	Common in children, crowded populations (jails, nursing homes); transmission through skin-to-skin contact (most common) or via fomites. Treatment: permethrin cream, washing/drying all clothing/bedding, treat close contacts.
Pediculus humanus/ Phthirus pubis  	Blood-sucking lice that cause intense pruritus with associated excoriations, commonly on scalp and neck (head lice) or waistband and axilla (body lice).	Can transmit *Rickettsia prowazekii* (epidemic typhus), *Borrelia recurrentis* (relapsing fever), *Bartonella quintana* (trench fever). Treatment includes pyrethroids, malathion, or ivermectin lotion, and nit B combing. Children with head lice can be treated at home without interrupting school attendance.

Parasite hints

ASSOCIATIONS	ORGANISM
Biliary tract disease, cholangiocarcinoma	*Clonorchis sinensis*
Brain cysts, seizures	*Taenia solium* (neurocysticercosis)
Hematuria, squamous cell bladder cancer	*Schistosoma haematobium*
Liver (hydatid) cysts	*Echinococcus granulosus*
Microcytic anemia	*Ancylostoma*, *Necator*
Myalgias, periorbital edema	*Trichinella spiralis*
Perianal pruritus	*Enterobius*
Portal hypertension	*Schistosoma mansoni*, *Schistosoma japonicum*
Vitamin B_{12} deficiency	*Diphyllobothrium latum*

▸ MICROBIOLOGY—VIROLOGY

Viral structure—general features


Naked virus with icosahedral capsid
Capsid
Nucleic acid
Enveloped virus with icosahedral capsid
Surface protein
Lipid bilayer
Capsid
Nucleic acid
Enveloped virus with helical capsid
Surface protein
Lipid bilayer
Helical nucleocapsid with integrated RNA

Viral genetics

Recombination	Exchange of genes between 2 chromosomes by crossing over within regions of significant base sequence homology.
Reassortment	When viruses with segmented genomes (eg, influenza virus) exchange genetic material. For example, the 2009 novel H1N1 influenza A pandemic emerged via complex viral reassortment of genes from human, swine, and avian viruses. Has potential to cause antigenic shift.
Complementation	When 1 of 2 viruses that infect the cell has a mutation that results in a nonfunctional protein, the nonmutated virus "complements" the mutated one by making a functional protein that serves both viruses. For example, hepatitis D virus requires the presence of replicating hepatitis B virus to supply HBsAg, the envelope protein for HDV.
Phenotypic mixing	Occurs with simultaneous infection of a cell with 2 viruses. Genome of virus A can be partially or completely coated (forming pseudovirion) with the surface proteins of virus B. Type B protein coat determines the tropism (infectivity) of the hybrid virus. However, the progeny from this infection have a type A coat that is encoded by its type A genetic material.

Viral vaccines

Live attenuated vaccines	**M**MR, **Y**ellow fever, **R**otavirus, **I**nfluenza (intranasal), **C**hickenpox (VZV), **S**mallpox, **S**abin polio virus.	"**M**usic and **LYRICSS** are best enjoyed **Live**." MMR = measles, mumps, rubella; live attenuated vaccine that can be given to HIV ⊕ patients who do not show signs of immunodeficiency.
Killed	**R**abies, **I**nfluenza (injected), Salk **P**olio, and H**A**V vaccines. Killed/inactivated vaccines induce only humoral immunity but are stable.	Sal**K** = **K**illed. **RIP A**lways.
Subunit	HBV (antigen = HBsAg), HPV (types 6, 11, 16, and 18).	

DNA viral genomes	All DNA viruses except the Parvoviridae are dsDNA. All are linear except papilloma-, polyoma-, and hepadnaviruses (circular).	All are dsDNA (like our cells), except "**part-of-a-virus**" (**parvovirus**) is ssDNA. *Parvus* = small.

RNA viral genomes

All RNA viruses except Reoviridae are ssRNA.
⊕ stranded RNA viruses: I went to a **retro** (**retro**virus) **toga** (**toga**virus) party, where I drank **flav**ored (**flav**ivirus) **Corona** (**corona**virus) and ate **hippie** (**hepe**virus) **Cali**fornia (**cali**civirus) **pic**kles (**pic**ornavirus).

All are ssRNA (like our mRNA), except "**re**peato-virus" (**reo**virus) is dsRNA.

Naked viral genome infectivity

Purified nucleic acids of most dsDNA (except poxviruses and HBV) and ⊕ strand ssRNA (≈ mRNA) viruses are infectious. Naked nucleic acids of ⊖ strand ssRNA and dsRNA viruses are not infectious. They require polymerases contained in the complete virion.

Viral replication

DNA viruses	All replicate in the nucleus (except poxvirus). "**Pox** is out of the **box** (nucleus)."
RNA viruses	All replicate in the cytoplasm (except influenza virus and retroviruses).

Viral envelopes

Naked (nonenveloped) viruses include **P**apillomavirus, **A**denovirus, **P**arvovirus, **P**olyomavirus, **C**alicivirus, **P**icornavirus, **R**eovirus, and **Hep**evirus.
Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions include herpesviruses, which acquire envelopes from nuclear membrane.

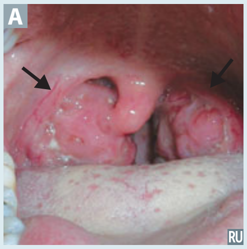
Give **PAPP** smears and **CPR** to a **naked hip**pie (**hep**evirus).
DNA = **PAPP**; RNA = **CPR** and **hep**evirus.

DNA virus characteristics

Some general rules—all DNA viruses:

GENERAL RULE	COMMENTS
Are **HHAPPPP**y viruses	**H**epadna, **H**erpes, **A**deno, **P**ox, **P**arvo, **P**apilloma, **P**olyoma.
Are double stranded	Except parvo (single stranded).
Have linear genomes	Except papilloma and polyoma (circular, supercoiled) and hepadna (circular, incomplete).
Are icosahedral	Except pox (complex).
Replicate in the nucleus	Except pox (carries own DNA-dependent RNA polymerase).

DNA viruses

VIRAL FAMILY	ENVELOPE	DNA STRUCTURE	MEDICAL IMPORTANCE
Herpesviruses	Yes	DS and linear	See Herpesviruses entry
Poxvirus	Yes	DS and linear (largest DNA virus)	Smallpox eradicated world wide by use of the live-attenuated vaccine Cowpox ("milkmaid blisters") **Molluscum contagiosum**—flesh-colored papule with central umbilication
Hepadnavirus	Yes	Partially DS and circular	HBV: ▪ Acute or chronic hepatitis ▪ Not a retrovirus but has reverse transcriptase
Adenovirus 	No	DS and linear	Febrile pharyngitis A—sore throat Acute hemorrhagic cystitis Pneumonia Conjunctivitis—"pink eye"
Papillomavirus	No	DS and circular	HPV–warts (serotypes 1, 2, 6, 11), CIN, cervical cancer (most commonly 16, 18)
Polyomavirus	No	DS and circular	JC virus—progressive multifocal leukoencephalopathy (PML) in HIV BK virus—transplant patients, commonly targets kidney **JC**: **J**unky **C**erebrum; **BK**: **B**ad **K**idney
Parvovirus	No	SS and linear (smallest DNA virus)	B19 virus—aplastic crises in sickle cell disease, "slapped cheek" rash in children (erythema infectiosum, or fifth disease) RBC destruction in fetus leads to hydrops fetalis and death, in adults leads to pure RBC aplasia and rheumatoid arthritis–like symptoms

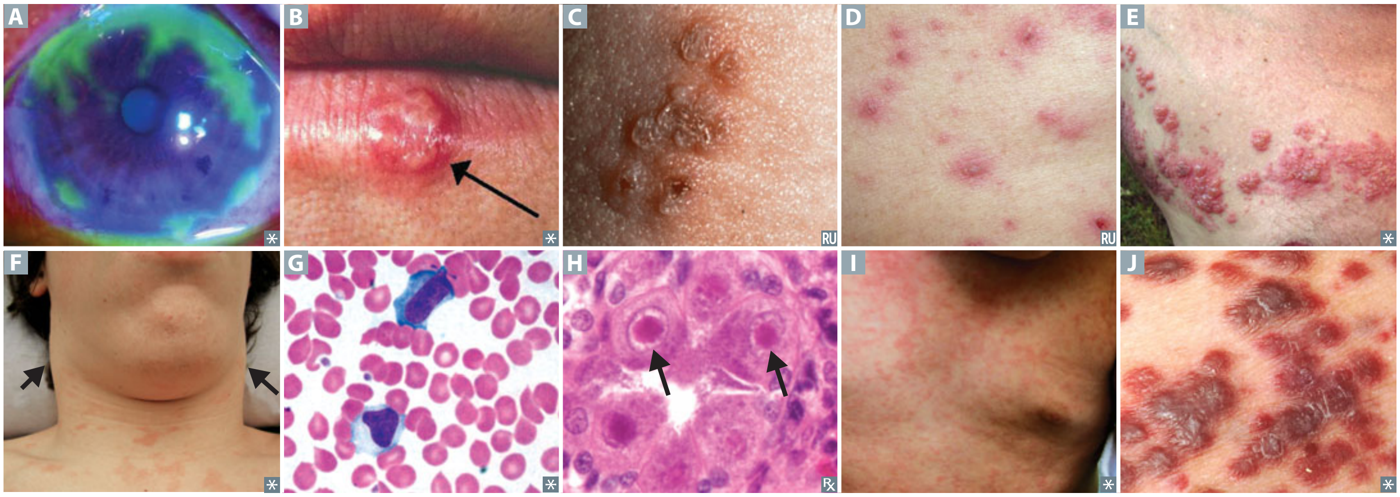
Herpesviruses

Enveloped, DS, and linear viruses

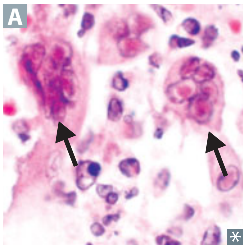
VIRUS	ROUTE OF TRANSMISSION	CLINICAL SIGNIFICANCE	NOTES
Herpes simplex virus-1	Respiratory secretions, saliva	Gingivostomatitis, keratoconjunctivitis A, herpes labialis B, herpetic whitlow on finger, temporal lobe encephalitis, esophagitis, erythema multiforme.	Most common cause of sporadic encephalitis, can present as altered mental status, seizures, and/or aphasia.
Herpes simplex virus-2	Sexual contact, perinatal	Herpes genitalis C, neonatal herpes.	Latent in sacral ganglia. Viral meningitis more common with HSV-2 than with HSV-1.
Varicella-Zoster virus (HHV-3)	Respiratory secretions	Varicella-zoster (chickenpox D, shingles E), encephalitis, pneumonia. Most common complication of shingles is post-herpetic neuralgia.	Latent in dorsal root or trigeminal ganglia; CN V_1 branch involvement can cause herpes zoster ophthalmicus.

Herpesviruses *(continued)*

VIRUS	ROUTE OF TRANSMISSION	CLINICAL SIGNIFICANCE	NOTES
Epstein-Barr virus (HHV-4)	Respiratory secretions, saliva; aka "kissing disease," (common in teens, young adults)	**Mononucleosis**—fever, hepatosplenomegaly, pharyngitis, and lymphadenopathy (especially posterior cervical nodes F). Avoid contact sports until resolution due to risk of splenic rupture. Associated with lymphomas (eg, endemic Burkitt lymphoma), nasopharyngeal carcinoma (especially Asian adults), lymphoproliferative disease in transplant patients.	Infects B cells through CD21. Atypical lymphocytes on peripheral blood smear G—not infected B cells but reactive cytotoxic T cells. ⊕ Monospot test—heterophile antibodies detected by agglutination of sheep or horse RBCs. Use of amoxicillin in mononucleosis can cause characteristic maculopapular rash.
Cytomegalovirus (HHV-5)	Congenital transfusion, sexual contact, saliva, urine, transplant	Mononucleosis (⊖ Monospot) in immunocompetent patients; infection in immunocompromised, especially pneumonia in transplant patients; esophagitis; AIDS **retinitis** ("**sight**omegalovirus"): hemorrhage, cotton-wool exudates, vision loss. Congenital CMV	Infected cells have characteristic "owl eye" inclusions H. Latent in mononuclear cells.
Human herpes-viruses 6 and 7	Saliva	Roseola infantum (exanthem subitum): high fevers for several days that can cause seizures, followed by diffuse macular rash I.	**Roseola**: fever first, **Ros**ie (cheeks) **la**ter. HHV-7—less common cause of roseola.
Human herpesvirus 8	Sexual contact	Kaposi sarcoma (neoplasm of endothelial cells). Seen in HIV/AIDS and transplant patients. Dark/violaceous plaques or nodules J representing vascular proliferations.	Can also affect GI tract and lungs.



HSV identification



Viral culture for skin/genitalia.
CSF PCR for herpes encephalitis.
Tzanck test—a smear of an opened skin vesicle to detect multinucleated giant cells A commonly seen in HSV-1, HSV-2, and VZV infection. PCR of skin lesions is currently test of choice.
Intranuclear eosinophilic Cowdry A inclusions also seen with HSV-1, HSV-2, VZV.
Tzanck heavens I do not have herpes.

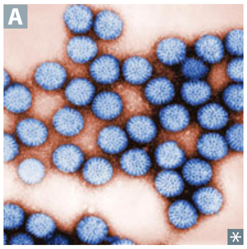
Receptors used by viruses

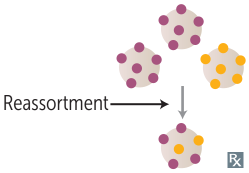
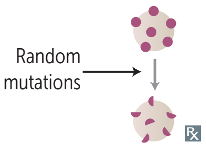
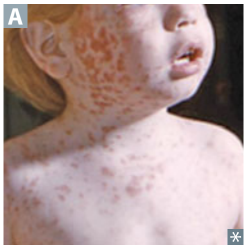
VIRUS	RECEPTORS
CMV	Integrins (heparan sulfate)
EBV	CD21
HIV	CD4, CXCR4, CCR5
Parvovirus B19	P antigen on RBCs
Rabies	Nicotinic AChR
Rhinovirus	ICAM-1

RNA viruses

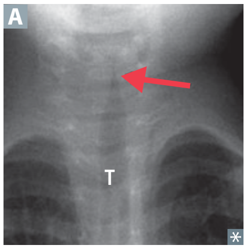
VIRAL FAMILY	ENVELOPE	RNA STRUCTURE	CAPSID SYMMETRY	MEDICAL IMPORTANCE
Reoviruses	No	DS linear 10–12 segments	Icosahedral (double)	Coltivirus[a]—Colorado tick fever Rotavirus—cause of fatal diarrhea in children
Picornaviruses	No	SS ⊕ linear	Icosahedral	**P**oliovirus—polio-Salk/Sabin vaccines—IPV/OPV **E**chovirus—aseptic meningitis **R**hinovirus—"common cold" **C**oxsackievirus—aseptic meningitis; herpangina (mouth blisters, fever); hand, foot, and mouth disease; myocarditis; pericarditis **H**AV—acute viral hepatitis **PERCH**
Hepevirus	No	SS ⊕ linear	Icosahedral	HEV
Caliciviruses	No	SS ⊕ linear	Icosahedral	Norovirus—viral gastroenteritis
Flaviviruses	Yes	SS ⊕ linear	Icosahedral	HCV Yellow fever[a] Dengue[a] St. Louis encephalitis[a] West Nile virus[a] (meningoencephalitis) Zika virus
Togaviruses	Yes	SS ⊕ linear	Icosahedral	Rubella Western and Eastern equine encephalitis[a] Chikungunya virus
Retroviruses	Yes	SS ⊕ linear 2 copies	Icosahedral (HTLV), complex and conical (HIV)	Have reverse transcriptase HTLV—T-cell leukemia HIV—AIDS
Coronaviruses	Yes	SS ⊕ linear	Helical	"Common cold," SARS, MERS
Orthomyxoviruses	Yes	SS ⊖ linear 8 segments	Helical	Influenza virus
Paramyxoviruses	Yes	SS ⊖ linear Nonsegmented	Helical	**P**a**R**a**M**yxovirus: **P**arainfluenza—croup **R**SV—bronchiolitis in babies; **R**x—**r**ibavirin **M**easles, **M**umps
Rhabdoviruses	Yes	SS ⊖ linear	Helical	Rabies
Filoviruses	Yes	SS ⊖ linear	Helical	Ebola/Marburg hemorrhagic fever—often fatal!
Arenaviruses	Yes	SS ⊕ and ⊖ circular 2 segments	Helical	LCMV—lymphocytic choriomeningitis virus Lassa fever encephalitis—spread by rodents
Bunyaviruses	Yes	SS ⊖ circular 3 segments	Helical	California encephalitis[a] Sandfly/Rift Valley fevers[a] Crimean-Congo hemorrhagic fever[a] Hantavirus—hemorrhagic fever, pneumonia
Delta virus	Yes	SS ⊖ circular	Uncertain	HDV is a "defective" virus that requires the presence of HBV to replicate

SS, single-stranded; DS, double-stranded; ⊕, positive sense; ⊖, negative sense; [a]= **arbo**virus, **ar**thropod **bo**rne (mosquitoes, ticks).

Negative-stranded viruses	Must transcribe ⊖ strand to ⊕. Virion brings its own RNA-dependent RNA polymerase. They include **A**renaviruses, **B**unyaviruses, **P**aramyxoviruses, **O**rthomyxoviruses, **F**iloviruses, and **R**habdoviruses.	**A**lways **B**ring **P**olymerase **O**r **F**ail **R**eplication.
Segmented viruses	All are RNA viruses. They include **B**unyaviruses, **O**rthomyxoviruses (influenza viruses), **A**renaviruses, and **R**eoviruses.	**BOAR**.
Picornavirus	Includes **P**oliovirus, **E**chovirus, **R**hinovirus, **C**oxsackievirus, and **HA**V. RNA is translated into 1 large polypeptide that is cleaved by proteases into functional viral proteins. Can cause aseptic (viral) meningitis (except rhinovirus and HAV). All are enteroviruses except rhinovirus.	Pico**RNA**virus = small **RNA** virus. **PERCH** on a "**peak**" (**pic**o).
Rhinovirus	A picornavirus. Nonenveloped RNA virus. Cause of common cold; > 100 serologic types. Acid labile—destroyed by stomach acid; therefore, does not infect the GI tract (unlike the other picornaviruses).	**Rhino** has a runny **nose**.
Yellow fever virus	A flavivirus (also an arbovirus) transmitted by *Aedes* mosquitoes. Virus has a monkey or human reservoir. Symptoms: high fever, black vomitus, and jaundice. May see Councilman bodies (eosinophilic apoptotic globules) on liver biopsy.	*Flavi* = yellow, jaundice.
Rotavirus 	Rotavirus A, the most important global cause of infantile gastroenteritis, is a segmented dsRNA virus (a reovirus). Major cause of acute diarrhea in the United States during winter, especially in day care centers, kindergartens. Villous destruction with atrophy leads to ↓ absorption of Na^+ and loss of K^+.	**ROTA**virus = **R**ight **O**ut **T**he **A**nus. CDC recommends routine vaccination of all infants.

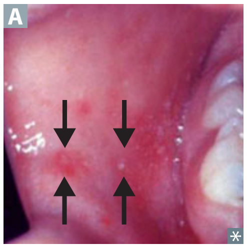
Influenza viruses	Orthomyxoviruses. Enveloped, ⊖ ssRNA viruses with 8-segment genome. Contain hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly *S aureus*, *S pneumoniae*, and *H influenzae*.	Reformulated vaccine ("the flu shot") contains viral strains most likely to appear during the flu season, due to the virus' rapid genetic change. Killed viral vaccine is most frequently used. Live attenuated vaccine contains temperature-sensitive mutant that replicates in the nose but not in the lung; administered intranasally.
Genetic shift/ antigenic shift  	Causes pandemics. Reassortment of viral genome segments, such as when segments of human flu A virus reassort with swine flu A virus.	**S**udden **s**hift is more deadly than gra**d**ual **d**rift.
Genetic drift/ antigenic drift  	Causes epidemics. Minor (antigenic drift) changes based on random mutation in hemagglutinin or neuraminidase genes.	
Rubella virus  	A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, confluent rash that starts on face and spreads centrifugally to involve trunk and extremities A. Causes mild disease in children but serious congenital disease (a ToRCHeS infection). Congenital rubella findings include "blueberry muffin" appearance due to dermal extramedullary hematopoiesis.	
Paramyxoviruses	Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup: seal-like barking cough), mumps, measles, RSV, and human metapneumovirus, which causes respiratory tract infection (bronchiolitis, pneumonia) in infants. All contain surface F (fusion) protein, which causes respiratory epithelial cells to fuse and form multinucleated cells. Palivizumab (monoclonal antibody against F protein) prevents pneumonia caused by RSV infection in premature infants. **P**alivizumab for **P**aramyxovirus (RSV) **P**rophylaxis in **P**remies.	

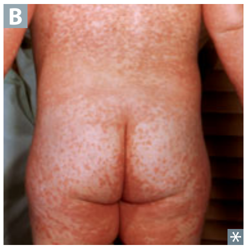
Croup (acute laryngotracheobronchitis)



Caused by parainfluenza viruses (paramyxovirus). Virus membrane contains hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Results in a "seal-like" barking cough and inspiratory stridor. Narrowing of upper trachea and subglottis leads to characteristic steeple sign on x-ray A. Severe croup can result in pulsus paradoxus 2° to upper airway obstruction.

Measles (rubeola) virus



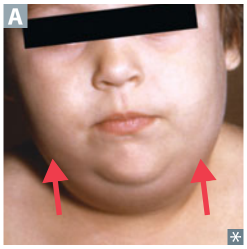


A paramyxovirus that causes measles. Usual presentation involves prodromal fever with cough, coryza, and conjunctivitis, then eventually Koplik spots (bright red spots with blue-white center on buccal mucosa A), followed 1–2 days later by a maculopapular rash B that starts at the head/neck and spreads downward. Lymphadenitis with Warthin-Finkeldey giant cells (fused lymphocytes) in a background of paracortical hyperplasia. SSPE (subacute sclerosing panencephalitis, occurring years later), encephalitis (1:2000), and giant cell pneumonia (rarely, in immunosuppressed) are possible sequelae.

3 C's of measles:
- **C**ough
- **C**oryza
- **C**onjunctivitis

Vitamin A supplementation can reduce morbidity and mortality from measles, particularly in malnourished children.

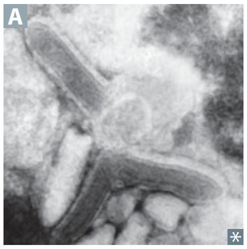
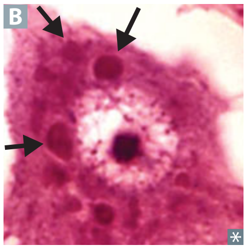
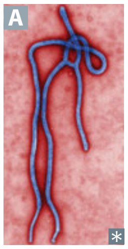
Mumps virus



A paramyxovirus that causes mumps, uncommon due to effectiveness of MMR vaccine.

Symptoms: **P**arotitis A, **O**rchitis (inflammation of testes), aseptic **M**eningitis, and **P**ancreatitis. Can cause sterility (especially after puberty).

Mumps makes your parotid glands and testes as big as **POM-P**oms.

Rabies virus  	Bullet-shaped virus A. Negri bodies (cytoplasmic inclusions B) commonly found in Purkinje cells of cerebellum and in hippocampal neurons. Rabies has long incubation period (weeks to months) before symptom onset. Postexposure prophylaxis is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. Example of passive-active immunity. Travels to the CNS by migrating in a retrograde fashion (via dynein motors) up nerve axons after binding to ACh receptors. Progression of disease: fever, malaise → agitation, photophobia, hydrophobia, hypersalivation → paralysis, coma → death.	Infection more commonly from bat, raccoon, and skunk bites than from dog bites in the United States; aerosol transmission (eg, bat caves) also possible.
Ebola virus 	A filovirus A that targets endothelial cells, phagocytes, hepatocytes. Following an incubation period of up to 21 days, presents with abrupt onset of flu-like symptoms, diarrhea/vomiting, high fever, myalgia. Can progress to DIC, diffuse hemorrhage, shock. Diagnosed with RT-PCR within 48 hr of symptom onset. High mortality rate.	Transmission requires direct contact with bodily fluids, fomites (including dead bodies), infected bats or primates (apes/monkeys); high incidence of nosocomial infection. Supportive care, no definitive treatment. Strict isolation of infected individuals and barrier practices for health care workers are key to preventing transmission.
Zika virus	A flavivirus most commonly transmitted by *Aedes* mosquito bites. Causes conjunctivitis, low-grade pyrexia, and itchy rash in 20% cases. Can lead to congenital microcephaly or miscarriages if transmitted in utero. Diagnose with RT-PCR or serology.	Sexual and vertical transmission possible. Outbreaks more common in tropical and subtropical climates. Supportive care, no definitive treatment.

Hepatitis viruses

Signs and symptoms of all hepatitis viruses: episodes of fever, jaundice, ↑ ALT and AST. Naked viruses (HAV and HEV) lack an envelope and are not destroyed by the gut: the **vowels** hit your **bowels**.

HBV DNA polymerase has DNA- and RNA-dependent activities. Upon entry into nucleus, the polymerase completes the partial dsDNA. Host RNA polymerase transcribes mRNA from viral DNA to make viral proteins. The DNA polymerase then reverse transcribes viral RNA to DNA, which is the genome of the progeny virus.

HCV lacks 3′-5′ exonuclease activity → no proofreading ability → variation in antigenic structures of HCV envelope proteins. Host antibody production lags behind production of new mutant strains of HCV.

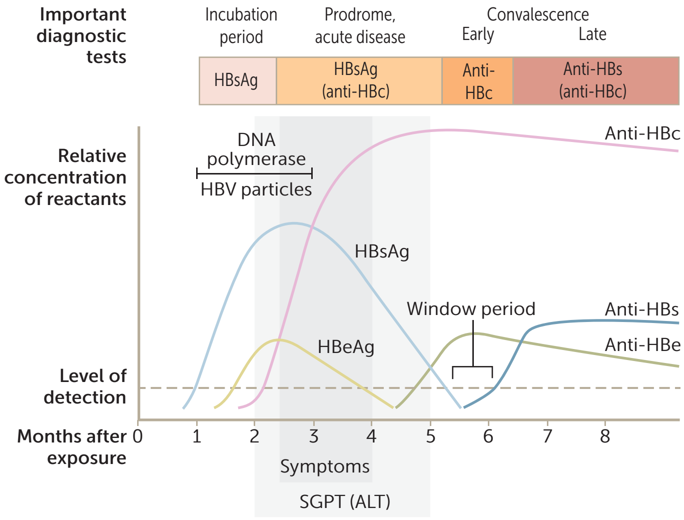
Virus	HAV	HBV	HCV	HDV	HEV
FAMILY	RNA picornavirus	DNA hepadnavirus	RNA flavivirus	RNA deltavirus	RNA hepevirus
TRANSMISSION	Fecal-oral (shellfish, travelers, day care)	Parenteral (**B**lood), sexual (**B**aby-making), perinatal (**B**irthing)	Primarily blood (IVDU, post-transfusion)	Parenteral, sexual, perinatal	Fecal-oral, especially waterborne
INCUBATION	Short (weeks)	Long (months)	Long	Superinfection (HDV after HBV) = short Coinfection (HDV with HBV) = long	Short
CLINICAL COURSE	**A**symptomatic (usually), **A**cute	Initially like serum sickness (fever, arthralgias, rash); may progress to carcinoma	May progress to **C**irrhosis or **C**arcinoma	Similar to HBV	Fulminant hepatitis in **E**xpectant (pregnant) women
PROGNOSIS	Good	Adults → mostly full resolution; neonates → worse prognosis	Majority develop stable, **C**hronic hepatitis **C**	Superinfection → worse prognosis	High mortality in pregnant women
HCC RISK	No	Yes	Yes	Yes	No
LIVER BIOPSY	Hepatocyte swelling, monocyte infiltration, Councilman bodies	Granular eosinophilic "ground glass" appearance; cytotoxic T cells mediate damage	Lymphoid aggregates with focal areas of macrovesicular steatosis	Similar to HBV	Patchy necrosis
NOTES	No carrier state ("**A**lone")	Carrier state common	Carrier state very common	**D**efective virus, **D**epends on HBV HBsAg	**E**nteric, **E**pidemic, no carrier state

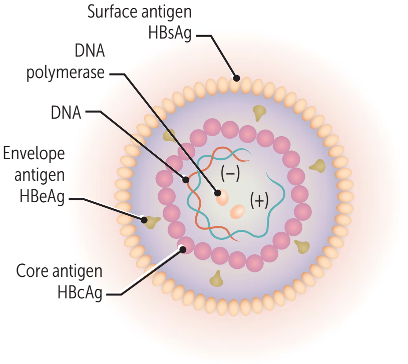
Extrahepatic manifestations of hepatitis B and C

	Hepatitis B	Hepatitis C
HEMATOLOGIC	Aplastic anemia	Essential mixed cryoglobulinemia, ↑ risk B-cell NHL, ITP, autoimmune hemolytic anemia
RENAL	Membranous GN → membranoproliferative GN	Membranoproliferative GN → membranous GN
VASCULAR	Polyarteritis nodosa	Leukocytoclastic vasculitis
DERMATOLOGIC		Sporadic porphyria cutanea tarda, lichen planus
ENDOCRINE		↑ risk of diabetes mellitus, autoimmune hypothyroidism

Hepatitis serologic markers

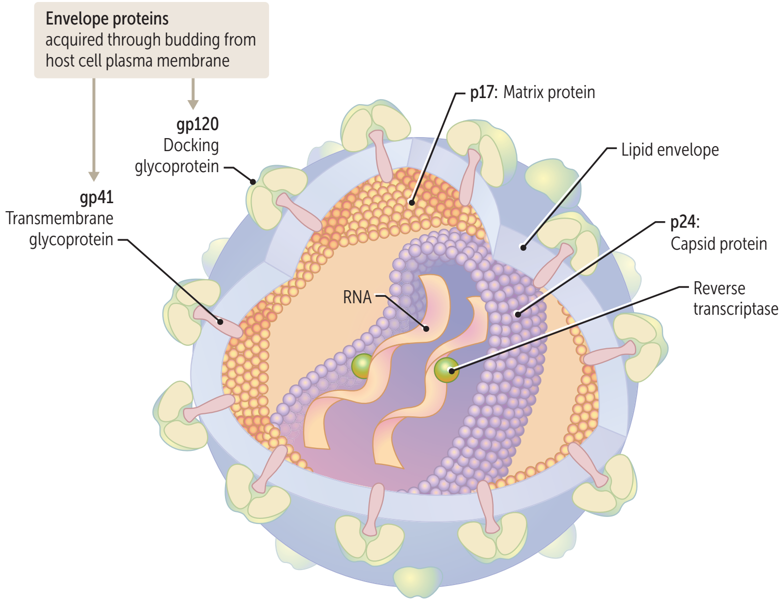
Anti-HAV (IgM)	IgM antibody to HAV; best test to detect acute hepatitis A.
Anti-HAV (IgG)	IgG antibody indicates prior HAV infection and/or prior vaccination; protects against reinfection.
HBsAg	Antigen found on surface of HBV; indicates hepatitis B infection.
Anti-HBs	Antibody to HBsAg; indicates immunity to hepatitis B due to vaccination or recovery from infection.
HBcAg	Antigen associated with core of HBV.
Anti-HBc	Antibody to HBcAg; IgM = acute/recent infection; IgG = prior exposure or chronic infection. IgM anti-HBc may be the sole ⊕ marker of infection during window period.
HBeAg	Secreted by infected hepatocyte into circulation. Not part of mature HBV virion. Indicates active viral replication and therefore high transmissibility and poorer prognosis.
Anti-HBe	Antibody to HBeAg; indicates low transmissibility.





	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc
Acute HBV	✓		✓		IgM
Window				✓	IgM
Chronic HBV (high infectivity)	✓		✓		IgG
Chronic HBV (low infectivity)	✓			✓	IgG
Recovery		✓		✓	IgG
Immunized		✓			

HIV


Envelope proteins
acquired through budding from host cell plasma membrane
gp120
Docking glycoprotein
gp41
Transmembrane glycoprotein
p17: Matrix protein
Lipid envelope
p24:
Capsid protein
RNA
Reverse transcriptase

Diploid genome (2 molecules of RNA).

The 3 structural genes (protein coded for):

- *env* (gp120 and gp41):
  - Formed from cleavage of gp160 to form envelope glycoproteins.
  - gp120—attachment to host CD4+ T cell.
  - gp41—fusion and entry.
- *gag* (p24 and p17)—capsid and matrix proteins, respectively.
- *pol*—reverse transcriptase, aspartate protease, integrase.

Reverse transcriptase synthesizes dsDNA from genomic RNA; dsDNA integrates into host genome.

Virus binds CD4 as well as a coreceptor, either CCR5 on macrophages (early infection) or CXCR4 on T cells (late infection).

Homozygous CCR5 mutation = immunity.

Heterozygous CCR5 mutation = slower course.

HIV diagnosis

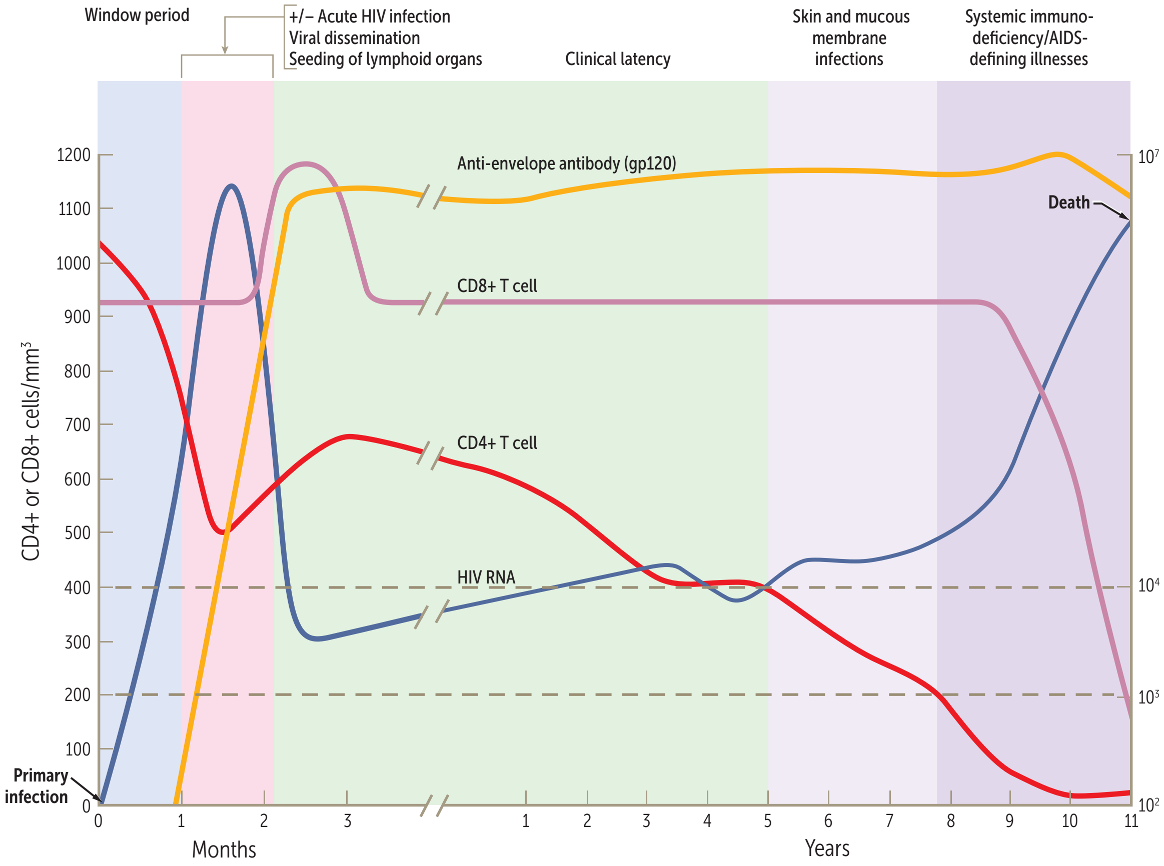
Presumptive diagnosis made with ELISA (sensitive, high false ⊕ rate and low threshold, **rule out** test); ⊕ results confirmed with Western blot assay (specific, low false ⊕ rate and high threshold, rule in test).

Viral load tests determine the amount of viral RNA in the plasma. High viral load associated with poor prognosis. Also use viral load to monitor effect of drug therapy. HIV genotyping used to determine appropriate therapy.

AIDS diagnosis ≤ 200 CD4+ cells/mm^3 (normal: 500–1500 cells/mm^3). HIV⊕ with AIDS-defining condition (eg, *Pneumocystis* pneumonia) or CD4+ percentage < 14%.

ELISA/Western blot tests look for antibodies to viral proteins; these tests often are falsely ⊖ in the first 1–2 months of HIV infection and falsely ⊕ initially in babies born to infected mothers (anti-gp120 crosses placenta). Use PCR in neonates to detect viral load.

Time course of untreated HIV infection



Dashed lines on CD4+ count axis indicate moderate immunocompromise (< 400 CD4+ cells/mm^3) and when AIDS-defining illnesses emerge (< 200 CD4+ cells/mm^3).

Most patients who do not receive treatment eventually die of complications of HIV infection.

Four stages of untreated infection:

1. **F**lu-like (acute)
2. **F**eeling fine (latent)
3. **F**alling count
4. **F**inal crisis

During clinical latency phase, virus replicates in lymph nodes

Common diseases of HIV-positive adults

As CD4+ cell count ↓, risks of reactivation of past infections (eg, TB, HSV, shingles), dissemination of bacterial infections and fungal infections (eg, coccidioidomycosis), and non-Hodgkin lymphomas ↑.

PATHOGEN	PRESENTATION	FINDINGS
CD4+ cell count < 500/mm^3		
Candida albicans	Oral thrush	Scrapable white plaque, pseudohyphae on microscopy
EBV	Oral hairy leukoplakia	Unscrapable white plaque on lateral tongue
Bartonella henselae	Bacillary angiomatosis	Biopsy with neutrophilic inflammation
HHV-8	Kaposi sarcoma	Biopsy with lymphocytic inflammation
HPV	Squamous cell carcinoma, commonly of anus (men who have sex with men) or cervix (women)	
CD4+ cell count < 200/mm^3		
Histoplasma capsulatum	Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea	Oval yeast cells within macrophages
HIV	Dementia	
JC virus (reactivation)	Progressive multifocal leukoencephalopathy	Nonenhancing areas of demyelination on MRI
Pneumocystis jirovecii	*Pneumocystis* pneumonia	“Ground-glass” opacities on CXR
CD4+ cell count < 100/mm^3		
Aspergillus fumigatus	Hemoptysis, pleuritic pain	Cavitation or infiltrates on chest imaging
Candida albicans	Esophagitis	White plaques on endoscopy; yeast and pseudohyphae on biopsy
CMV	Retinitis, esophagitis, colitis, pneumonitis, encephalitis	Linear ulcers on endoscopy, cotton-wool spots on fundoscopy Biopsy reveals cells with intranuclear (owl eye) inclusion bodies
Cryptococcus neoformans	Meningitis	Encapsulated yeast on India ink stain or capsular antigen ⊕
Cryptosporidium spp.	Chronic, watery diarrhea	Acid-fast oocysts in stool
EBV	B-cell lymphoma (eg, non-Hodgkin lymphoma, CNS lymphoma)	CNS lymphoma—ring enhancing, may be solitary (vs *Toxoplasma*)
Mycobacterium avium–intracellulare, Mycobacterium avium complex	Nonspecific systemic symptoms (fever, night sweats, weight loss) or focal lymphadenitis	
Toxoplasma gondii	Brain abscesses	Multiple ring-enhancing lesions on MRI

Prions

Prion diseases are caused by the conversion of a normal (predominantly α-helical) protein termed prion protein (PrP^c) to a β-pleated form (PrP^{sc}), which is transmissible via CNS-related tissue (iatrogenic CJD) or food contaminated by BSE-infected animal products (variant CJD). PrP^{sc} resists protease degradation and facilitates the conversion of still more PrP^c to PrP^{sc}. Resistant to standard sterilizing procedures, including standard autoclaving. Accumulation of PrP^{sc} results in spongiform encephalopathy and dementia, ataxia, and death.

Creutzfeldt-Jakob disease—rapidly progressive dementia, typically sporadic (some familial forms).

Bovine spongiform encephalopathy (BSE)—also known as "mad cow disease."

Kuru—acquired prion disease noted in tribal populations practicing human cannibalism.

▶ MICROBIOLOGY—SYSTEMS

Normal flora: dominant

LOCATION	MICROORGANISM
Skin	*S epidermidis*
Nose	*S epidermidis*; colonized by *S aureus*
Oropharynx	Viridans group streptococci
Dental plaque	*S mutans*
Colon	*B fragilis* > *E coli*
Vagina	*Lactobacillus*, colonized by *E coli* and group B strep

Neonates delivered by C-section have no flora but are rapidly colonized after birth.

Bugs causing food-borne illness

S aureus and *B cereus* food poisoning starts quickly and ends quickly.

MICROORGANISM	SOURCE OF INFECTION
B cereus	Reheated rice. "Food poisoning from reheated rice? Be serious!" (*B cereus*)
C botulinum	Improperly canned foods (toxins), raw honey (spores)
C perfringens	Reheated meat
E coli O157:H7	Undercooked meat
L monocytogenes	Deli meats, soft cheeses
Salmonella	Poultry, meat, and eggs
S aureus	Meats, mayonnaise, custard; preformed toxin
V parahaemolyticus and *V vulnificus*[a]	Contaminated seafood

[a] *V vulnificus* can also cause wound infections from contact with contaminated water or shellfish.

Bugs causing diarrhea

Bloody diarrhea	
Campylobacter	Comma- or S-shaped organisms; growth at 42°C
E histolytica	Protozoan; amebic dysentery; liver abscess
Enterohemorrhagic *E coli*	O157:H7; can cause HUS; makes Shiga-like toxin
Enteroinvasive *E coli*	Invades colonic mucosa
Salmonella (non-typhoidal)	Lactose ⊖; flagellar motility; has animal reservoir, especially poultry and eggs
Shigella	Lactose ⊖; very low ID_{50}; produces Shiga toxin (human reservoir only); bacillary dysentery
Y enterocolitica	Day care outbreaks, pseudoappendicitis
Watery diarrhea	
C difficile	Pseudomembranous colitis; associated with antibiotics and PPIs; occasionally bloody diarrhea
C perfringens	Also causes gas gangrene
Enterotoxigenic *E coli*	Travelers' diarrhea; produces heat-labile (LT) and heat-stable (ST) toxins
Protozoa	*Giardia*, *Cryptosporidium*
V cholerae	Comma-shaped organisms; rice-water diarrhea; often from infected seafood
Viruses	Rotavirus, norovirus, adenovirus

Common causes of pneumonia

NEONATES (< 4 WK)	CHILDREN (4 WK–18 YR)	ADULTS (18–40 YR)	ADULTS (40–65 YR)	ELDERLY
Group B streptococci *E coli*	Viruses (RSV) *Mycoplasma* *C trachomatis* (infants–3 yr) *C pneumoniae* (school-aged children) *S pneumoniae* Runts May Cough Chunky Sputum	*Mycoplasma* *C pneumoniae* *S pneumoniae* Viruses (eg, influenza)	*S pneumoniae* *H influenzae* Anaerobes Viruses *Mycoplasma*	*S pneumoniae* Influenza virus Anaerobes *H influenzae* Gram ⊖ rods

Special groups	
Alcoholic	*Klebsiella*, anaerobes usually due to aspiration (eg, *Peptostreptococcus*, *Fusobacterium*, *Prevotella*, *Bacteroides*)
IV drug users	*S pneumoniae*, *S aureus*
Aspiration	Anaerobes
Atypical	*Mycoplasma*, *Legionella*, *Chlamydia*
Cystic fibrosis	*Pseudomonas*, *S aureus*, *S pneumoniae*, *Burkholderia cepacia*
Immunocompromised	*S aureus*, enteric gram ⊖ rods, fungi, viruses, *P jirovecii* (with HIV)
Nosocomial (hospital acquired)	*S aureus*, *Pseudomonas*, other enteric gram ⊖ rods
Postviral	*S pneumoniae*, *S aureus*, *H influenzae*

Common causes of meningitis

NEWBORN (0–6 MO)	CHILDREN (6 MO–6 YR)	6–60 YR	60 YR +
Group B streptococci *E coli* *Listeria*	*S pneumoniae* *N meningitidis* *H influenzae* type B Enteroviruses	*S pneumoniae* *N meningitidis* (#1 in teens) Enteroviruses HSV	*S pneumoniae* Gram ⊖ rods *Listeria*

Give ceftriaxone and vancomycin empirically (add ampicillin if *Listeria* is suspected).

Viral causes of meningitis: enteroviruses (especially coxsackievirus), HSV-2 (HSV-1 = encephalitis), HIV, West Nile virus (also causes encephalitis), VZV.

In HIV: *Cryptococcus* spp.

Note: Incidence of *H influenzae* meningitis has ↓ greatly due to conjugate *H influenzae* vaccinations. Today, cases are usually seen in unimmunized children.

CSF findings in meningitis

	OPENING PRESSURE	CELL TYPE	PROTEIN	GLUCOSE
Bacterial	↑	↑ PMNs	↑	↓
Fungal/TB	↑	↑ lymphocytes	↑	↓
Viral	Normal/↑	↑ lymphocytes	Normal/↑	Normal

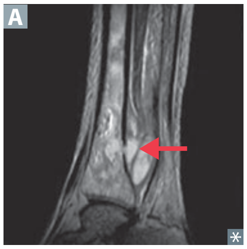
Infections causing brain abscess

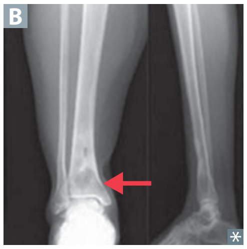
Most commonly viridans streptococci and *Staphylococcus aureus*. If dental infection or extraction precedes abscess, oral anaerobes commonly involved.

Multiple abscesses are usually from bacteremia; single lesions from contiguous sites: otitis media and mastoiditis → temporal lobe and cerebellum; sinusitis or dental infection → frontal lobe.

Toxoplasma reactivation in AIDS.

Osteomyelitis





RISK FACTOR	ASSOCIATED INFECTION
Assume if no other information is available	*S aureus* (most common overall)
Sexually active	*Neisseria gonorrhoeae* (rare), septic arthritis more common
Sickle cell disease	*Salmonella* and *S aureus*
Prosthetic joint replacement	*S aureus* and *S epidermidis*
Vertebral involvement	*S aureus*, *Mycobacterium tuberculosis* (Pott disease)
Cat and dog bites	*Pasteurella multocida*
IV drug abuse	*Pseudomonas*, *Candida*, *S aureus* are most common

Elevated C-reactive protein (CRP) and erythrocyte sedimentation rate common but nonspecific.

MRI is best for detecting acute infection and detailing anatomic involvement A. Radiographs are insensitive early but can be useful in chronic osteomyelitis B.

Urinary tract infections

Cystitis presents with dysuria, frequency, urgency, suprapubic pain, and WBCs (but not WBC casts) in urine. Primarily caused by ascension of microbes from urethra to bladder. Males—infants with congenital defects, vesicoureteral reflux. Elderly—enlarged prostate. Ascension to kidney results in pyelonephritis, which presents with fever, chills, flank pain, costovertebral angle tenderness, hematuria, and WBC casts.

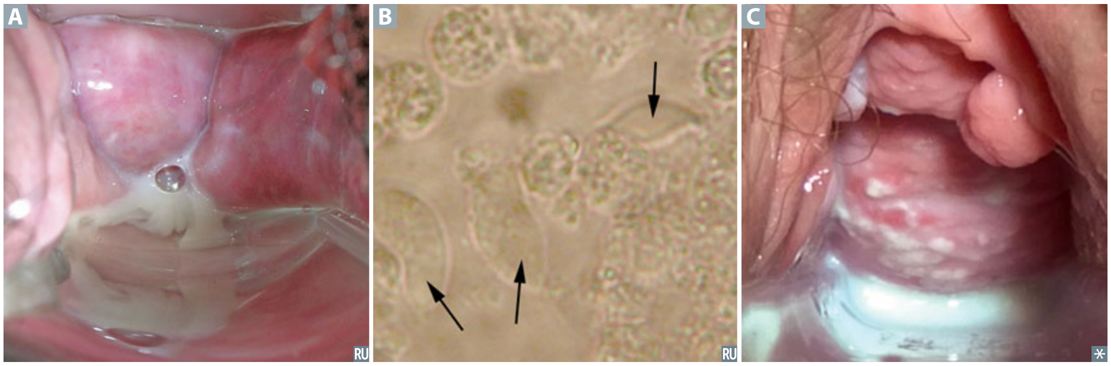
Ten times more common in women (shorter urethras colonized by fecal flora). Other predisposing factors: obstruction, kidney surgery, catheterization, GU malformation, diabetes, pregnancy.

UTI bugs

SPECIES	FEATURES	COMMENTS
Escherichia coli	Leading cause of UTI. Colonies show green metallic sheen on EMB agar.	Diagnostic markers: ⊕ Leukocyte esterase = evidence of WBC activity. ⊕ Nitrite test = reduction of urinary nitrates by bacterial species (eg, *E coli*). ⊕ Urease test = urease-producing bugs (eg, *S saprophyticus*, *Proteus*, *Klebsiella*).
Staphylococcus saprophyticus	2nd leading cause of UTI in sexually active women.	
Klebsiella pneumoniae	3rd leading cause of UTI. Large mucoid capsule and viscous colonies.	
Serratia marcescens	Some strains produce a red pigment; often nosocomial and drug resistant.	
Enterococcus	Often nosocomial and drug resistant.	
Proteus mirabilis	Motility causes "swarming" on agar; produces urease; associated with struvite stones.	
Pseudomonas aeruginosa	Blue-green pigment and fruity odor; usually nosocomial and drug resistant.	

Common vaginal infections

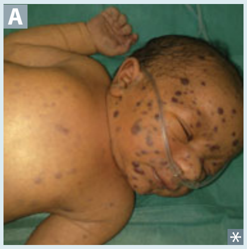
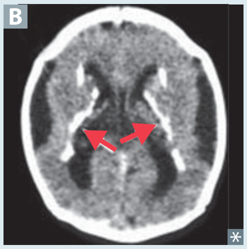
	Bacterial vaginosis	***Trichomonas* vaginitis**	***Candida* vulvovaginitis**
SIGNS AND SYMPTOMS	No inflammation Thin, white discharge A with fishy odor	Inflammation ("strawberry cervix") Frothy, yellow-green, foul-smelling discharge	Inflammation Thick, white, "cottage cheese" discharge C
LAB FINDINGS	Clue cells pH > 4.5	Motile trichomonads B pH > 4.5	Pseudohyphae pH normal (4.0–4.5)
TREATMENT	Metronidazole	Metronidazole Treat sexual partner(s)	-azoles



ToRCHeS infections

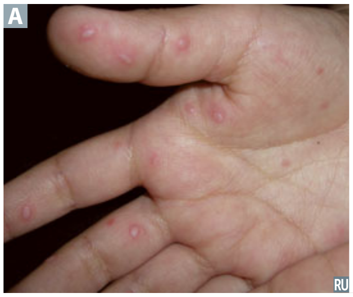
Microbes that may pass from mother to fetus. Transmission is transplacental in most cases, or via delivery (especially HSV-2). Nonspecific signs common to many **ToRCHeS** infections include hepatosplenomegaly, jaundice, thrombocytopenia, and growth retardation.

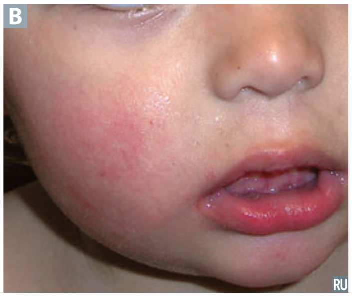
Other important infectious agents include *Streptococcus agalactiae* (group B streptococci), *E coli*, and *Listeria monocytogenes*—all causes of meningitis in neonates. Parvovirus B19 causes hydrops fetalis.

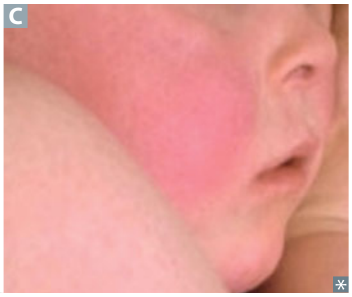
AGENT	MODES OF MATERNAL TRANSMISSION	MATERNAL MANIFESTATIONS	NEONATAL MANIFESTATIONS
***To**xoplasma gondii*  	Cat feces or ingestion of undercooked meat	Usually asymptomatic; lymphadenopathy (rarely)	Classic triad: chorioretinitis, hydrocephalus, and intracranial calcifications, +/– “blueberry muffin” rash A.
Rubella	Respiratory droplets	Rash, lymphadenopathy, polyarthritis, polyarthralgia	Classic triad: abnormalities of **eye** (cataract) and **ear** (deafness) and congenital **heart** disease (PDA); ± “blueberry muffin” rash. “**I** (eye) ♥ **ruby** (**rub**ella) **ear**rings.”
Cytomegalovirus  	Sexual contact, organ transplants	Usually asymptomatic; mononucleosis-like illness	Hearing loss, seizures, petechial rash, “blueberry muffin” rash, periventricular calcifications B
HIV	Sexual contact, needlestick	Variable presentation depending on CD4+ cell count	Recurrent infections, chronic diarrhea
Herpes simplex virus-2	Skin or mucous membrane contact	Usually asymptomatic; herpetic (vesicular) lesions	Meningoencephalitis, herpetic (vesicular) lesions
Syphilis	Sexual contact	Chancre (1°) and disseminated rash (2°) are the two stages likely to result in fetal infection	Often results in stillbirth, hydrops fetalis; if child survives, presents with facial abnormalities (eg, notched teeth, saddle nose, short maxilla), saber shins, CN VIII deafness

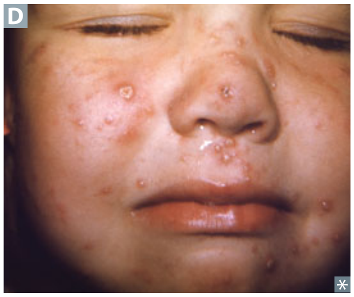
Red rashes of childhood

AGENT	ASSOCIATED SYNDROME/DISEASE	CLINICAL PRESENTATION
Coxsackievirus type A	Hand-foot-mouth disease	Oval-shaped vesicles on palms and soles A; vesicles and ulcers in oral mucosa
Human herpesvirus 6	Roseola (exanthem subitum)	Asymptomatic rose-colored macules appear on body after several days of high fever; can present with febrile seizures; usually affects infants
Measles virus	Measles (rubeola)	Confluent rash beginning at head and moving down; preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa
Parvovirus B19	Erythema infectiosum (fifth disease)	"Slapped cheek" rash on face B (can cause hydrops fetalis in pregnant women)
Rubella virus	Rubella (German measles)	Pink macules and papules begin at head and move down, remain discrete → fine desquamating truncal rash; postauricular lymphadenopathy
Streptococcus pyogenes	Scarlet fever	Erythematous, sandpaper-like rash C with fever and sore throat
Varicella-Zoster virus	Chickenpox	Vesicular rash begins on trunk; spreads to face D and extremities with lesions of different stages

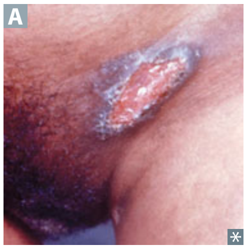




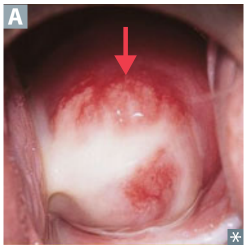


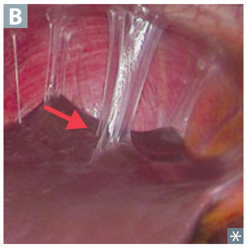


Sexually transmitted infections

DISEASE	CLINICAL FEATURES	ORGANISM
AIDS	Opportunistic infections, Kaposi sarcoma, lymphoma	HIV
Chancroid	Painful genital ulcer with exudate, inguinal adenopathy	*Haemophilus* ***ducreyi*** (it's so painful, you "**do cry**")
Chlamydia	Urethritis, cervicitis, epididymitis, conjunctivitis, reactive arthritis, PID	*Chlamydia trachomatis* (D–K)
Condylomata acuminata	Genital warts, koilocytes	HPV-6 and -11
Genital herpes	Painful penile, vulvar, or cervical vesicles and ulcers; can cause systemic symptoms such as fever, headache, myalgia	HSV-2, less commonly HSV-1
Gonorrhea	Urethritis, cervicitis, PID, prostatitis, epididymitis, arthritis, creamy purulent discharge	*Neisseria gonorrhoeae*
Granuloma inguinale (Donovanosis)  	Painless, beefy red ulcer that bleeds readily on contact A Not common in US	*Klebsiella (Calymmatobacterium) granulomatis;* cytoplasmic Donovan bodies (bipolar staining) seen on microscopy
Hepatitis B	Jaundice	HBV
Lymphogranuloma venereum	Infection of lymphatics; painless genital ulcers, painful lymphadenopathy (ie, buboes)	*C trachomatis* (L1–L3)
Primary syphilis	Painless chancre	*Treponema pallidum*
Secondary syphilis	Fever, lymphadenopathy, skin rashes, condylomata lata	
Tertiary syphilis	Gummas, tabes dorsalis, general paresis, aortitis, Argyll Robertson pupil	
Trichomoniasis	Vaginitis, strawberry cervix, motile in wet prep	*Trichomonas vaginalis*

Pelvic inflammatory disease





Top bugs—*Chlamydia trachomatis* (subacute, often undiagnosed), *Neisseria gonorrhoeae* (acute). *C trachomatis*—most common bacterial STI in the United States. Cervical motion tenderness (chandelier sign), purulent cervical discharge A. PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.

Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions.

Can lead to **Fitz-Hugh–Curtis syndrome**—infection of the liver capsule and "violin string" adhesions of peritoneum to liver B.

Nosocomial infections

E coli (UTI) and *S aureus* (wound infection) are the two most common causes.

RISK FACTOR	PATHOGEN	UNIQUE SIGNS/SYMPTOMS
Antibiotic use	*Clostridium difficile*	Watery diarrhea, leukocytosis
Aspiration (2° to altered mental status, old age)	Polymicrobial, gram ⊖ bacteria, often anaerobes	Right lower lobe infiltrate or right upper/middle lobe (patient recumbent); purulent malodorous sputum
Decubitus ulcers, surgical wounds, drains	*S aureus* (including MRSA), gram ⊖ anaerobes (*Bacteroides*, *Prevotella*, *Fusobacterium*)	Erythema, tenderness, induration, drainage from surgical wound sites
Intravascular catheters	*S aureus* (including MRSA), *S epidermidis* (long term), *Enterobacter*	Erythema, induration, tenderness, drainage from access sites
Mechanical ventilation, endotracheal intubation	Late onset: *P aeruginosa*, *Klebsiella*, *Acinetobacter*, *S aureus*	New infiltrate on CXR, ↑ sputum production; sweet odor (*Pseudomonas*)
Renal dialysis unit, needlestick	HBV, HCV	
Urinary catheterization	*E coli*, *Klebsiella*, *Proteus* spp.	Dysuria, leukocytosis, flank pain or costovertebral angle tenderness
Water aerosols	*Legionella*	Signs of pneumonia, GI symptoms (nausea, vomiting), neurologic abnormalities

Bugs affecting unvaccinated children

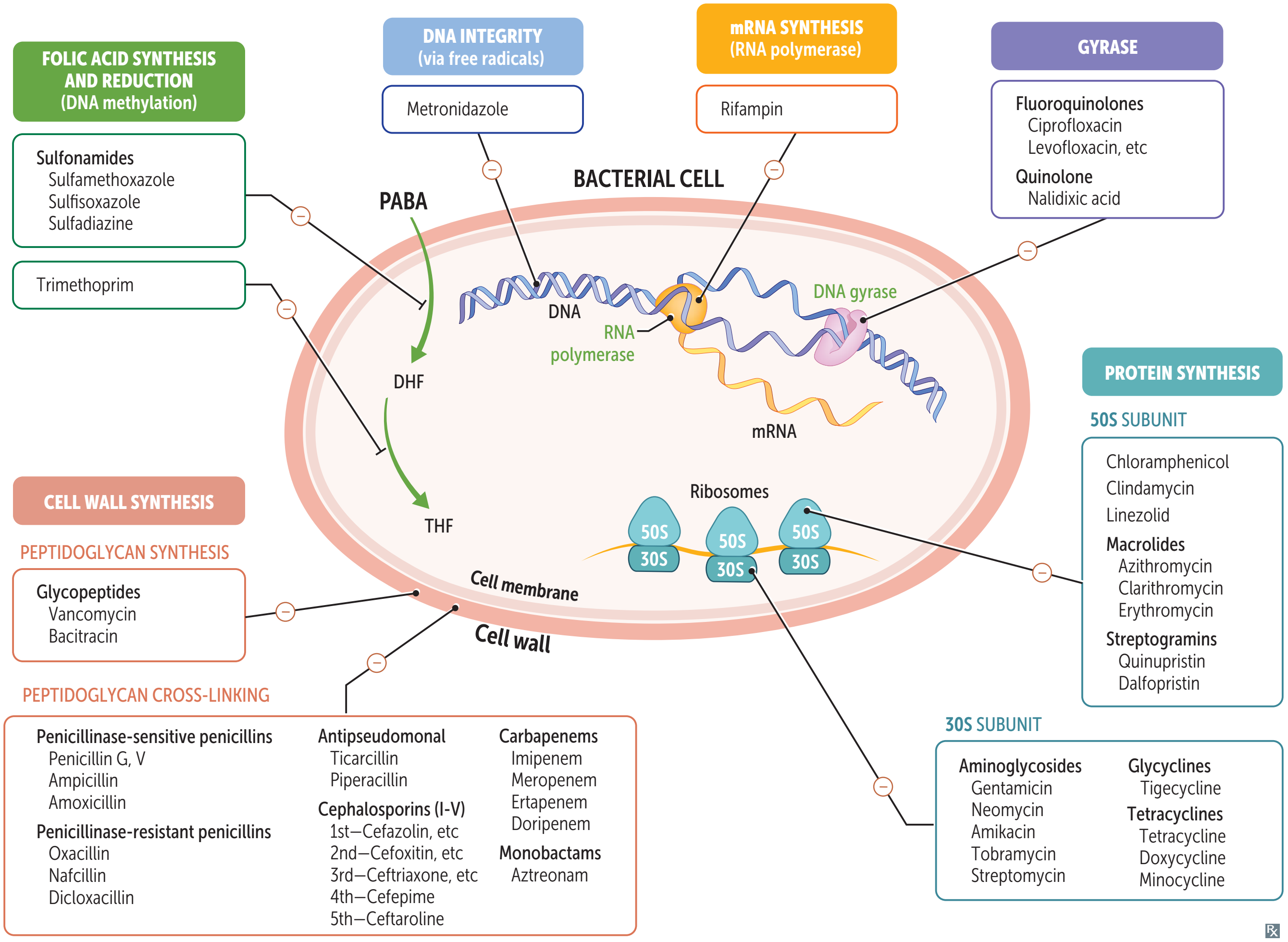
CLINICAL PRESENTATION	FINDINGS/LABS	PATHOGEN
Dermatologic		
Rash	Beginning at head and moving down with postauricular lymphadenopathy	Rubella virus
	Beginning at head and moving down; rash preceded by cough, coryza, conjunctivitis, and blue-white (Koplik) spots on buccal mucosa	Measles virus
Neurologic		
Meningitis	Microbe colonizes nasopharynx	*H influenzae* type B
	Can also lead to myalgia and paralysis	Poliovirus
Respiratory		
Epiglottitis	Fever with dysphagia, drooling, and difficulty breathing due to edematous "cherry red" epiglottis; "thumbprint sign" on x-ray	*H influenzae* type B (also capable of causing epiglottitis in fully immunized children)
Pharyngitis	Grayish oropharyngeal exudate ("pseudomembranes" may obstruct airway); painful throat	*Corynebacterium diphtheriae* (elaborates toxin that causes necrosis in pharynx, cardiac, and CNS tissue)

Bug hints (if all else fails)

CHARACTERISTIC	ORGANISM
Asplenic patient (due to surgical splenectomy or autosplenectomy, eg, chronic sickle cell disease)	Encapsulated microbes, especially **SHiN** (**S** *pneumoniae* >> **H** *influenzae* type B > **N** *meningitidis*)
Branching rods in oral infection, sulfur granules	*Actinomyces israelii*
Chronic granulomatous disease	Catalase ⊕ microbes, especially *S aureus*
"Currant jelly" sputum	*Klebsiella*
Dog or cat bite	*Pasteurella multocida*
Facial nerve palsy (typically bilateral)	*Borrelia burgdorferi* (Lyme disease)
Fungal infection in diabetic or immunocompromised patient	*Mucor* or *Rhizopus* spp.
Health care provider	HBV (from needlestick)
Neutropenic patients	*Candida albicans* (systemic), *Aspergillus*
Organ transplant recipient	CMV
PAS ⊕	*Tropheryma whipplei* (Whipple disease)
Pediatric infection	*Haemophilus influenzae* (including epiglottitis)
Pneumonia in cystic fibrosis, burn infection	*Pseudomonas aeruginosa*
Pus, empyema, abscess	*S aureus*
Rash on hands and feet	Coxsackie A virus, *Treponema pallidum*, *Rickettsia rickettsii*
Sepsis/meningitis in newborn	Group B strep
Surgical wound	*S aureus*
Traumatic open wound	*Clostridium perfringens*

▶ MICROBIOLOGY—ANTIMICROBIALS

Antimicrobial therapy


FOLIC ACID SYNTHESIS AND REDUCTION (DNA methylation)
Sulfonamides
Sulfamethoxazole
Sulfisoxazole
Sulfadiazine
Trimethoprim
DNA INTEGRITY (via free radicals)
Metronidazole
mRNA SYNTHESIS (RNA polymerase)
Rifampin
GYRASE
Fluoroquinolones
Ciprofloxacin
Levofloxacin, etc
Quinolone
Nalidixic acid
BACTERIAL CELL
PABA
DHF
THF
DNA
RNA polymerase
DNA gyrase
mRNA
Ribosomes
50S
30S
Cell membrane
Cell wall
PROTEIN SYNTHESIS
50S SUBUNIT
Chloramphenicol
Clindamycin
Linezolid
Macrolides
Azithromycin
Clarithromycin
Erythromycin
Streptogramins
Quinupristin
Dalfopristin
30S SUBUNIT
Aminoglycosides
Gentamicin
Neomycin
Amikacin
Tobramycin
Streptomycin
Glycyclines
Tigecycline
Tetracyclines
Tetracycline
Doxycycline
Minocycline
CELL WALL SYNTHESIS
PEPTIDOGLYCAN SYNTHESIS
Glycopeptides
Vancomycin
Bacitracin
PEPTIDOGLYCAN CROSS-LINKING
Penicillinase-sensitive penicillins
Penicillin G, V
Ampicillin
Amoxicillin
Penicillinase-resistant penicillins
Oxacillin
Nafcillin
Dicloxacillin
Antipseudomonal
Ticarcillin
Piperacillin
Cephalosporins (I-V)
1st—Cefazolin, etc
2nd—Cefoxitin, etc
3rd—Ceftriaxone, etc
4th—Cefepime
5th—Ceftaroline
Carbapenems
Imipenem
Meropenem
Ertapenem
Doripenem
Monobactams
Aztreonam

Penicillin G, V	Penicillin G (IV and IM form), penicillin V (oral). Prototype β-lactam antibiotics.
MECHANISM	D-Ala-D-Ala structural analog. Bind penicillin-binding proteins (transpeptidases). Block transpeptidase cross-linking of peptidoglycan in cell wall. Activate autolytic enzymes.
CLINICAL USE	Mostly used for gram ⊕ organisms (*S pneumoniae*, *S pyogenes*, *Actinomyces*). Also used for gram ⊖ cocci (mainly *N meningitidis*) and spirochetes (namely *T pallidum*). Bactericidal for gram ⊕ cocci, gram ⊕ rods, gram ⊖ cocci, and spirochetes. Penicillinase sensitive.
ADVERSE EFFECTS	Hypersensitivity reactions, direct Coombs ⊕ hemolytic anemia.
RESISTANCE	Penicillinase in bacteria (a type of β-lactamase) cleaves β-lactam ring.

Penicillinase-sensitive penicillins	Amoxicillin, ampicillin; aminopenicillins.	
MECHANISM	Same as penicillin. Wider spectrum; penicillinase sensitive. Also combine with clavulanic acid to protect against destruction by β-lactamase.	**AM**ino**P**enicillins are **AMP**ed-up penicillin. Am**O**xicillin has greater **O**ral bioavailability than ampicillin.
CLINICAL USE	Extended-spectrum penicillin—***H** influenzae*, ***H** pylori*, ***E** coli*, ***L**isteria monocytogenes*, ***P**roteus mirabilis*, ***S**almonella*, ***S**higella*, enterococci.	Coverage: ampicillin/amoxicillin **HHELPSS** kill enterococci.
ADVERSE EFFECTS	Hypersensitivity reactions; rash; pseudomembranous colitis.	
MECHANISM OF RESISTANCE	Penicillinase in bacteria (a type of β-lactamase) cleaves β-lactam ring.	

Penicillinase-resistant penicillins	Dicloxacillin, nafcillin, oxacillin.	
MECHANISM	Same as penicillin. Narrow spectrum; penicillinase resistant because bulky R group blocks access of β-lactamase to β-lactam ring.	
CLINICAL USE	S *aureus* (except MRSA; resistant because of altered penicillin-binding protein target site).	"Use **naf** (nafcillin) for **staph**."
ADVERSE EFFECTS	Hypersensitivity reactions, interstitial nephritis.	

Antipseudomonal penicillins	Piperacillin, ticarcillin.
MECHANISM	Same as penicillin. Extended spectrum.
CLINICAL USE	*Pseudomonas* spp. and gram ⊖ rods; susceptible to penicillinase; use with β-lactamase inhibitors.
ADVERSE EFFECTS	Hypersensitivity reactions.

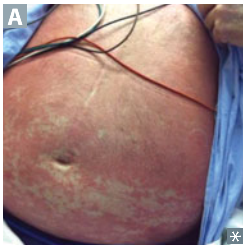
β-lactamase inhibitors	Include **C**lavulanic acid, **A**vibactam, **S**ulbactam, **T**azobactam. Often added to penicillin antibiotics to protect the antibiotic from destruction by β-lactamase (penicillinase).	**CAST**.

Cephalosporins (generations I–V)

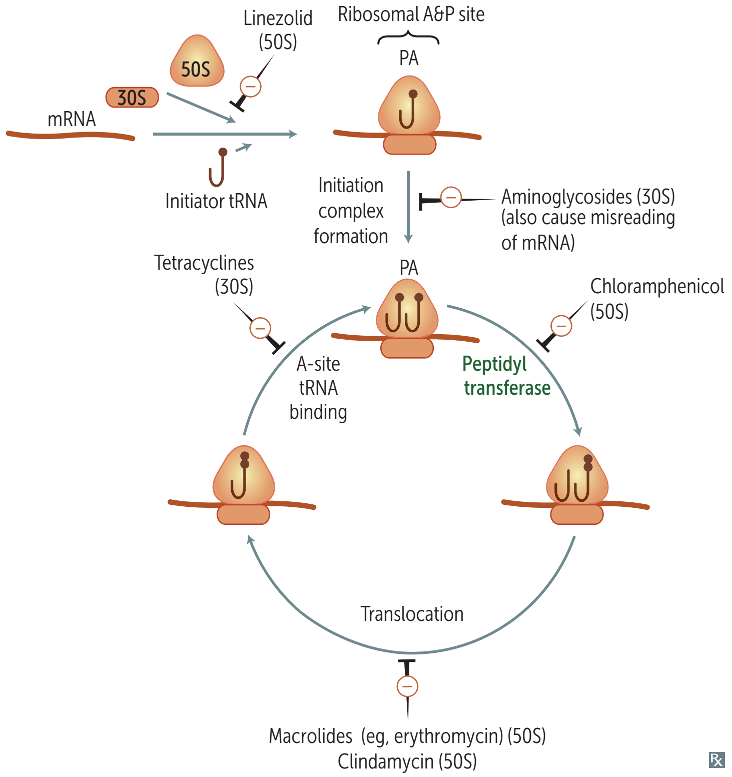
MECHANISM	β-lactam drugs that inhibit cell wall synthesis but are less susceptible to penicillinases. Bactericidal.	Organisms typically not covered by 1st–4th generation cephalosporins are **LAME**: *__L__isteria*, **A**typicals (*Chlamydia*, *Mycoplasma*), **M**RSA, and **E**nterococci.
CLINICAL USE	1st generation (cefazolin, cephalexin)—gram ⊕ cocci, *__P__roteus mirabilis*, *__E__ coli*, *__K__lebsiella pneumoniae*. Cefazolin used prior to surgery to prevent *S aureus* wound infections.	1st generation—**PEcK**.
	2nd generation (ce**fa**clor, ce**fox**itin, ce**fur**oxime)—gram ⊕ cocci, *__H__ influenzae*, *__E__nterobacter aerogenes*, *__N__eisseria* spp., *__S__erratia marcescens*, *__P__roteus mirabilis*, *__E__ coli*, *__K__lebsiella pneumoniae*.	**Fa**ke **fox** **fur**. 2nd generation—**HENS PEcK**.
	3rd generation (ceftriaxone, cefotaxime, cefpodoxime, ceftazidime)—serious gram ⊖ infections resistant to other β-lactams.	Can cross blood-brain barrier. Ceftriaxone—meningitis, gonorrhea, disseminated Lyme disease. Ceftazidime—*Pseudomonas*.
	4th generation (cefepime)—gram ⊖ organisms, with ↑ activity against *Pseudomonas* and gram ⊕ organisms.	
	5th generation (ceftaroline)—broad gram ⊕ and gram ⊖ organism coverage; unlike 1st–4th generation cephalosporins, ceftaroline covers *Listeria*, MRSA, and *Enterococcus faecalis*—does not cover *Pseudomonas*.	
ADVERSE EFFECTS	Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Low rate of cross-reactivity even in penicillin-allergic patients. ↑ nephrotoxicity of aminoglycosides.	
MECHANISM OF RESISTANCE	Structural change in penicillin-binding proteins (transpeptidases).	

Carbapenems	Imipenem, meropenem, ertapenem, doripenem.	
MECHANISM	Imipenem is a broad-spectrum, β-lactamase–resistant carbapenem. Always administered with cilastatin (inhibitor of renal dehydropeptidase I) to ↓ inactivation of drug in renal tubules.	With imipenem, "the kill is **lastin'** with ci**lastatin**." Newer carbapenems include ertapenem (limited *Pseudomonas* coverage) and doripenem.
CLINICAL USE	Gram ⊕ cocci, gram ⊖ rods, and anaerobes. Wide spectrum, but significant side effects limit use to life-threatening infections or after other drugs have failed. Meropenem has a ↓ risk of seizures and is stable to dehydropeptidase I.	
ADVERSE EFFECTS	GI distress, skin rash, and CNS toxicity (seizures) at high plasma levels.	

Monobactams	Aztreonam
MECHANISM	Less susceptible to β-lactamases. Prevents peptidoglycan cross-linking by binding to penicillin-binding protein 3. Synergistic with aminoglycosides. No cross-allergenicity with penicillins.
CLINICAL USE	Gram ⊖ rods only—no activity against gram ⊕ rods or anaerobes. For penicillin-allergic patients and those with renal insufficiency who cannot tolerate aminoglycosides.
ADVERSE EFFECTS	Usually nontoxic; occasional GI upset.

Vancomycin	
MECHANISM	Inhibits cell wall peptidoglycan formation by binding D-ala D-ala portion of cell wall precursors. Bactericidal against most bacteria (bacteriostatic against *C difficile*). Not susceptible to β-lactamases.
CLINICAL USE	Gram ⊕ bugs only—serious, multidrug-resistant organisms, including MRSA, *S epidermidis*, sensitive *Enterococcus* species, and *Clostridium difficile* (oral dose for pseudomembranous colitis).
ADVERSE EFFECTS 	Well tolerated in general—but **NOT** trouble free. **N**ephrotoxicity, **O**totoxicity, **T**hrombophlebitis, diffuse flushing—red man syndrome A (largely preventable by pretreatment with antihistamines and slow infusion rate).
MECHANISM OF RESISTANCE	Occurs in bacteria (eg, *Enterococcus*) via amino acid modification of **D-Ala-D-Ala** to D-Ala-D-Lac. "Pay back **2 D-Ala**s (dollars) for **van**dalizing (**van**comycin)."

Protein synthesis inhibitors


Linezolid
(50S)
Ribosomal A&P site
PA
50S
30S
mRNA
Initiator tRNA
Initiation
complex
formation
Aminoglycosides (30S)
(also cause misreading
of mRNA)
Tetracyclines
(30S)
PA
Chloramphenicol
(50S)
A-site
tRNA
binding
Peptidyl
transferase
Translocation
Macrolides (eg, erythromycin) (50S)
Clindamycin (50S)

Specifically target smaller bacterial ribosome (70S, made of 30S and 50S subunits), leaving human ribosome (80S) unaffected.

30S inhibitors

A = Aminoglycosides [bactericidal]
T = Tetracyclines [bacteriostatic]

50S inhibitors

C = Chloramphenicol, Clindamycin [bacteriostatic]
E = Erythromycin (macrolides) [bacteriostatic]
L = Linezolid [variable]
"Buy AT 30, CCEL (sell) at 50."

Aminoglycosides	Gentamicin, Neomycin, Amikacin, Tobramycin, Streptomycin.	"Mean" (aminoglycoside) GNATS caNNOT kill anaerobes.
MECHANISM	Bactericidal; irreversible inhibition of initiation complex through binding of the 30S subunit. Can cause misreading of mRNA. Also block translocation. Require O_2 for uptake; therefore ineffective against anaerobes.	
CLINICAL USE	Severe gram ⊖ rod infections. Synergistic with β-lactam antibiotics. Neomycin for bowel surgery.	
ADVERSE EFFECTS	Nephrotoxicity, Neuromuscular blockade, Ototoxicity (especially when used with loop diuretics). Teratogen.	
MECHANISM OF RESISTANCE	Bacterial transferase enzymes inactivate the drug by acetylation, phosphorylation, or adenylation.	

Tetracyclines	Tetracycline, doxycycline, minocycline.
MECHANISM	Bacteriostatic; bind to 30S and prevent attachment of aminoacyl-tRNA; limited CNS penetration. Doxycycline is fecally eliminated and can be used in patients with renal failure. Do not take tetracyclines with milk (Ca^{2+}), antacids (Ca^{2+} or Mg^{2+}), or iron-containing preparations because divalent cations inhibit drugs' absorption in the gut.
CLINICAL USE	*Borrelia burgdorferi*, *M pneumoniae*. Drugs' ability to accumulate intracellularly makes them very effective against *Rickettsia* and *Chlamydia*. Also used to treat acne. Doxycycline effective against MRSA.
ADVERSE EFFECTS	GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity. Contraindicated in pregnancy.
MECHANISM OF RESISTANCE	↓ uptake or ↑ efflux out of bacterial cells by plasmid-encoded transport pumps.

Glycylcyclines	Tigecycline.
MECHANISM	Tetracycline derivative. Binds to 30S, inhibiting protein synthesis. Generally bacteriostatic.
CLINICAL USE	Broad-spectrum anaerobic, gram ⊖, and gram ⊕ coverage. Multidrug-resistant (MRSA, VRE) organisms or infections requiring deep tissue penetration.
ADVERSE EFFECTS	GI symptoms: nausea, vomiting.

Chloramphenicol	
MECHANISM	Blocks peptidyltransferase at 50S ribosomal subunit. Bacteriostatic.
CLINICAL USE	Meningitis (*Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*) and Rocky Mountain spotted fever (*Rickettsia rickettsii*). Limited use owing to toxicities but often still used in developing countries because of low cost.
ADVERSE EFFECTS	Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronyltransferase).
MECHANISM OF RESISTANCE	Plasmid-encoded acetyltransferase inactivates the drug.

Clindamycin		
MECHANISM	Blocks peptide transfer (translocation) at 50S ribosomal subunit. Bacteriostatic.	
CLINICAL USE	Anaerobic infections (eg, *Bacteroides* spp., *Clostridium perfringens*) in aspiration pneumonia, lung abscesses, and oral infections. Also effective against invasive group A streptococcal infection.	Treats anaerobic infections **above** the diaphragm vs metronidazole (anaerobic infections **below** diaphragm).
ADVERSE EFFECTS	Pseudomembranous colitis (*C difficile* overgrowth), fever, diarrhea.	

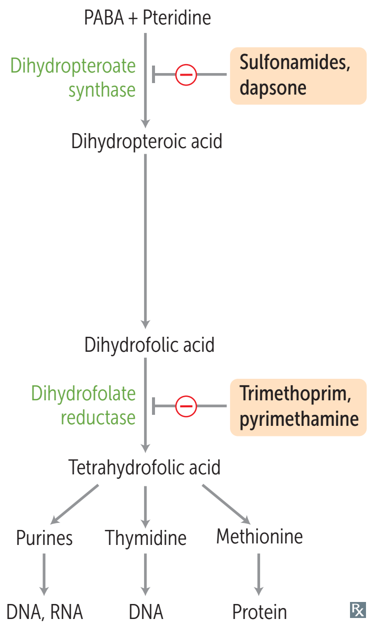
Oxazolidinones	Linezolid.
MECHANISM	Inhibit protein synthesis by binding to 50S subunit and preventing formation of the initiation complex.
CLINICAL USE	Gram ⊕ species including MRSA and VRE.
ADVERSE EFFECTS	Bone marrow suppression (especially thrombocytopenia), peripheral neuropathy, serotonin syndrome.
MECHANISM OF RESISTANCE	Point mutation of ribosomal RNA.

Macrolides	Azithromycin, clarithromycin, erythromycin.
MECHANISM	Inhibit protein synthesis by blocking translocation (“macro**slides**”); bind to the 23S rRNA of the 50S ribosomal subunit. Bacteriostatic.
CLINICAL USE	Atypical pneumonias (*Mycoplasma*, *Chlamydia*, *Legionella*), STIs (*Chlamydia*), gram ⊕ cocci (streptococcal infections in patients allergic to penicillin), and *B pertussis*.
ADVERSE EFFECTS	**MACRO**: Gastrointestinal **M**otility issues, **A**rrhythmia caused by prolonged QT interval, acute **C**holestatic hepatitis, **R**ash, e**O**sinophilia. Increases serum concentration of theophylline, oral anticoagulants. Clarithromycin and erythromycin inhibit cytochrome P-450.
MECHANISM OF RESISTANCE	Methylation of 23S rRNA-binding site prevents binding of drug.

Sulfonamides

Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine.

MECHANISM	Inhibit dihydropteroate synthase, thus inhibiting folate synthesis. Bacteriostatic (bactericidal when combined with trimethoprim).
CLINICAL USE	Gram ⊕, gram ⊖, *Nocardia*. SMX for simple UTI.
ADVERSE EFFECTS	Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), photosensitivity, Stevens-Johnson syndrome, kernicterus in infants, displace other drugs from albumin (eg, warfarin).
MECHANISM OF RESISTANCE	Altered enzyme (bacterial dihydropteroate synthase), ↓ uptake, or ↑ PABA synthesis.


PABA + Pteridine
Dihydropteroate synthase
Sulfonamides, dapsone
Dihydropteroic acid
Dihydrofolic acid
Dihydrofolate reductase
Trimethoprim, pyrimethamine
Tetrahydrofolic acid
Purines
Thymidine
Methionine
DNA, RNA
DNA
Protein

Dapsone

MECHANISM	Similar to sulfonamides, but structurally distinct agent.
CLINICAL USE	Leprosy (lepromatous and tuberculoid), *Pneumocystis jirovecii* prophylaxis.
ADVERSE EFFECTS	Hemolysis if G6PD deficient.

Trimethoprim

MECHANISM	Inhibits bacterial dihydrofolate reductase. Bacteriostatic.
CLINICAL USE	Used in combination with sulfonamides (trimethoprim-sulfamethoxazole [TMP-SMX]), causing sequential block of folate synthesis. Combination used for UTIs, *Shigella*, *Salmonella*, *Pneumocystis jirovecii* pneumonia treatment and prophylaxis, toxoplasmosis prophylaxis.
ADVERSE EFFECTS	Megaloblastic anemia, leukopenia, granulocytopenia. (May alleviate with supplemental folinic acid). **TMP T**reats **M**arrow **P**oorly.

Fluoroquinolones	Ciprofloxacin, norfloxacin, levofloxacin, ofloxacin, moxifloxacin, gemifloxacin, enoxacin.	
MECHANISM	Inhibit prokaryotic enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. Bactericidal. Must not be taken with antacids.	
CLINICAL USE	Gram ⊖ rods of urinary and GI tracts (including *Pseudomonas*), some gram ⊕ organisms, otitis externa.	
ADVERSE EFFECTS	GI upset, superinfections, skin rashes, headache, dizziness. Less commonly, can cause leg cramps and myalgias. Contraindicated in pregnant women, nursing mothers, and children < 18 years old due to possible damage to cartilage. Some may prolong QT interval. May cause tendonitis or tendon rupture in people > 60 years old and in patients taking prednisone. Ciprofloxacin inhibits cytochrome P-450.	Fluoroquino**lones** hurt attachments to your **bones**.
MECHANISM OF RESISTANCE	Chromosome-encoded mutation in DNA gyrase, plasmid-mediated resistance, efflux pumps.	

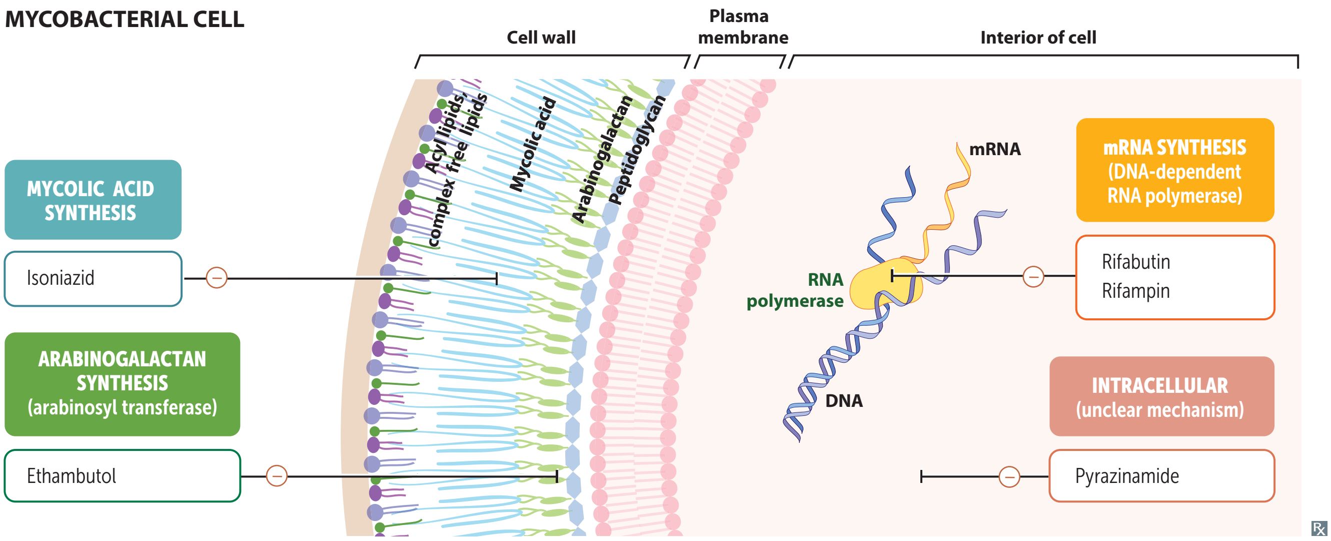
Daptomycin		
MECHANISM	Lipopeptide that disrupts cell membranes of gram ⊕ cocci by creating transmembrane channels.	
CLINICAL USE	*S aureus* skin infections (especially MRSA), bacteremia, endocarditis, VRE.	Not used for pneumonia (avidly binds to and is inactivated by surfactant).
ADVERSE EFFECTS	Myopathy, rhabdomyolysis.	

Metronidazole		
MECHANISM	Forms toxic free radical metabolites in the bacterial cell that damage DNA. Bactericidal, antiprotozoal.	
CLINICAL USE	Treats ***G**iardia*, ***E**ntamoeba*, ***T**richomonas*, ***G**ardnerella vaginalis*, **A**naerobes (*Bacteroides*, *C difficile*). Can be used in place of amoxicillin in *H **p**ylori* "triple therapy" in case of penicillin allergy.	**GET GAP** on the **Metro** with **metro**nidazole! Treats anaerobic infection **below** the diaphragm vs clindamycin (anaerobic infections **above** diaphragm).
ADVERSE EFFECTS	Disulfiram-like reaction (severe flushing, tachycardia, hypotension) with alcohol; headache, metallic taste.	

Antimycobacterial drugs

BACTERIUM	PROPHYLAXIS	TREATMENT
M tuberculosis	Isoniazid	**R**ifampin, **I**soniazid, **P**yrazinamide, **E**thambutol (**RIPE** for treatment)
M avium–intracellulare	Azithromycin, rifabutin	More drug resistant than *M tuberculosis*. Azithromycin or clarithromycin + ethambutol. Can add rifabutin or ciprofloxacin.
M leprae	N/A	Long-term treatment with dapsone and rifampin for tuberculoid form. Add clofazimine for lepromatous form.

MYCOBACTERIAL CELL


Cell wall
Plasma membrane
Interior of cell
Acyl lipids, complex free lipids
Mycolic acid
Arabinogalactan
Peptidoglycan
MYCOLIC ACID SYNTHESIS
Isoniazid
ARABINOGALACTAN SYNTHESIS (arabinosyl transferase)
Ethambutol
mRNA
RNA polymerase
DNA
mRNA SYNTHESIS (DNA-dependent RNA polymerase)
Rifabutin
Rifampin
INTRACELLULAR (unclear mechanism)
Pyrazinamide
℞

Rifamycins	Rifampin, rifabutin.	
MECHANISM	Inhibit DNA-dependent RNA polymerase.	**R**ifampin's **4 R's**: **R**NA polymerase inhibitor **R**amps up microsomal cytochrome P-450 **R**ed/orange body fluids **R**apid resistance if used alone **R**if**amp**in **ramp**s up cytochrome P-450, **but** rifa**but**in does not.
CLINICAL USE	*Mycobacterium tuberculosis*; delay resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with *Haemophilus influenzae* type B.	
ADVERSE EFFECTS	Minor hepatotoxicity and drug interactions (↑ cytochrome P-450); orange body fluids (nonhazardous side effect). Rifabutin favored over rifampin in patients with HIV infection due to less cytochrome P-450 stimulation.	
MECHANISM OF RESISTANCE	Mutations reduce drug binding to RNA polymerase. Monotherapy rapidly leads to resistance.	

Isoniazid

MECHANISM	↓ synthesis of mycolic acids. Bacterial catalase-peroxidase (encoded by KatG) needed to convert INH to active metabolite.	
CLINICAL USE	*Mycobacterium tuberculosis*. The only agent used as solo prophylaxis against TB. Also used as monotherapy for latent TB.	Different INH half-lives in fast vs slow acetylators.
ADVERSE EFFECTS	Hepatotoxicity, P-450 inhibition, drug-induced SLE, anion gap metabolic acidosis, vitamin B_6 deficiency (peripheral neuropathy, sideroblastic anemia). Administer with pyridoxine (B_6).	**INH I**njures **N**eurons and **H**epatocytes.
MECHANISM OF RESISTANCE	Mutations leading to underexpression of KatG.	

Pyrazinamide

MECHANISM	Mechanism uncertain. Pyrazinamide is a prodrug that is converted to the active compound pyrazinoic acid. Works best at acidic pH (eg, in host phagolysosomes).
CLINICAL USE	*Mycobacterium tuberculosis*.
ADVERSE EFFECTS	Hyperuricemia, hepatotoxicity.

Ethambutol

MECHANISM	↓ carbohydrate polymerization of mycobacterium cell wall by blocking arabinosyltransferase.
CLINICAL USE	*Mycobacterium tuberculosis*.
ADVERSE EFFECTS	**Optic** neuropathy (red-green color blindness). Pronounce "**eye**thambutol."

Streptomycin

MECHANISM	Interferes with 30S component of ribosome.
CLINICAL USE	*Mycobacterium tuberculosis* (2nd line).
ADVERSE EFFECTS	Tinnitus, vertigo, ataxia, nephrotoxicity.

Antimicrobial prophylaxis

CLINICAL SCENARIO	MEDICATION
High risk for endocarditis and undergoing surgical or dental procedures	Amoxicillin
Exposure to gonorrhea	Ceftriaxone
History of recurrent UTIs	TMP-SMX
Exposure to meningococcal infection	Ceftriaxone, ciprofloxacin, or rifampin
Pregnant woman carrying group B strep	Intrapartum penicillin G or ampicillin
Prevention of gonococcal conjunctivitis in newborn	Erythromycin ointment on eyes
Prevention of postsurgical infection due to *S aureus*	Cefazolin
Prophylaxis of strep pharyngitis in child with prior rheumatic fever	Benzathine penicillin G or oral penicillin V
Exposure to syphilis	Benzathine penicillin G

Prophylaxis in HIV patients

CELL COUNT	PROPHYLAXIS	INFECTION
CD4 < 200 cells/mm^3	TMP-SMX	*Pneumocystis* pneumonia
CD4 < 100 cells/mm^3	TMP-SMX	*Pneumocystis* pneumonia and toxoplasmosis
CD4 < 50 cells/mm^3	Azithromycin or clarithromycin	*Mycobacterium avium* complex

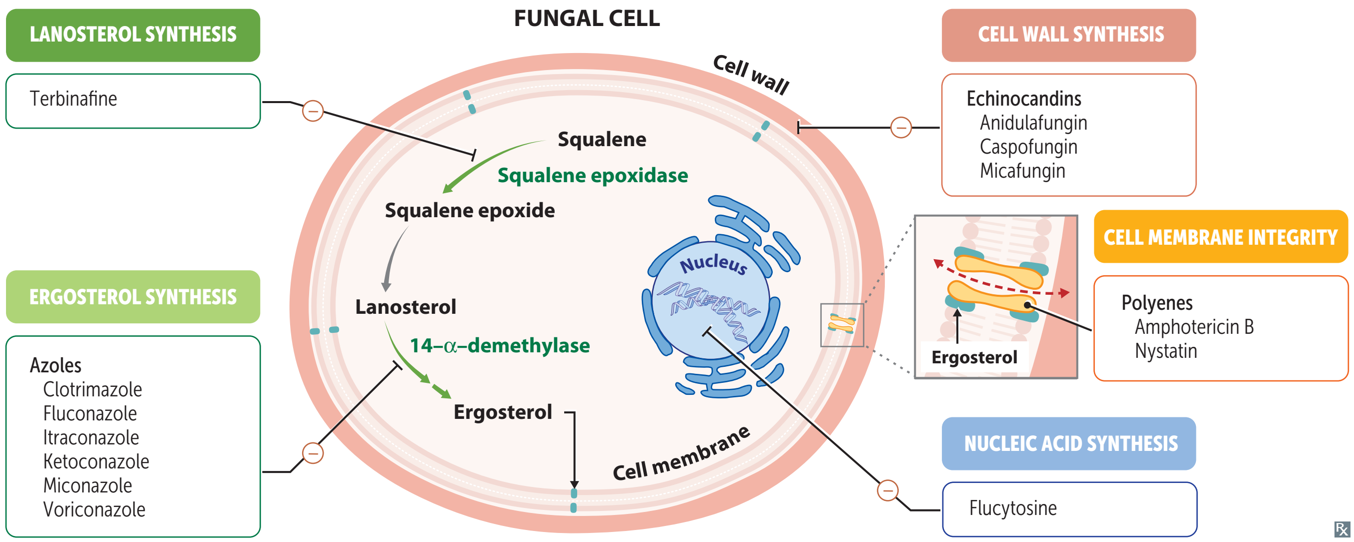
Treatment of highly resistant bacteria

MRSA: vancomycin, daptomycin, linezolid, tigecycline, ceftaroline, doxycycline.

VRE: linezolid and streptogramins (quinupristin, dalfopristin).

Multidrug-resistant *P aeruginosa*, multidrug-resistant *Acinetobacter baumannii*: polymyxins B and E (colistin).

Antifungal therapy


LANOSTEROL SYNTHESIS
Terbinafine
ERGOSTEROL SYNTHESIS
Azoles
Clotrimazole
Fluconazole
Itraconazole
Ketoconazole
Miconazole
Voriconazole
FUNGAL CELL
Cell wall
Squalene
Squalene epoxidase
Squalene epoxide
Lanosterol
14–α–demethylase
Ergosterol
Nucleus
Cell membrane
CELL WALL SYNTHESIS
Echinocandins
Anidulafungin
Caspofungin
Micafungin
CELL MEMBRANE INTEGRITY
Ergosterol
Polyenes
Amphotericin B
Nystatin
NUCLEIC ACID SYNTHESIS
Flucytosine
–
–
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Amphotericin B

MECHANISM	Binds ergosterol (unique to fungi); forms membrane pores that allow leakage of electrolytes.	Ampho**ter**icin “**tear**s” holes in the fungal membrane by forming pores.
CLINICAL USE	Serious, systemic mycoses. *Cryptococcus* (amphotericin B with/without flucytosine for cryptococcal meningitis), *Blastomyces*, *Coccidioides*, *Histoplasma*, *Candida*, *Mucor*. Intrathecally for fungal meningitis. Supplement K^+ and Mg^{2+} because of altered renal tubule permeability.	
ADVERSE EFFECTS	Fever/chills (“shake and bake”), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis (“**amphoterri**ble”). Hydration ↓ nephrotoxicity. Liposomal amphotericin ↓ toxicity.	

Nystatin

MECHANISM	Same as amphotericin B. Topical use only as too toxic for systemic use.
CLINICAL USE	“Swish and swallow” for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis.

Flucytosine

MECHANISM	Inhibits DNA and RNA biosynthesis by conversion to 5-fluorouracil by cytosine deaminase.
CLINICAL USE	Systemic fungal infections (especially meningitis caused by *Cryptococcus*) in combination with amphotericin B.
ADVERSE EFFECTS	Bone marrow suppression.

Azoles

Clotrimazole, fluconazole, itraconazole, ketoconazole, miconazole, voriconazole, isavuconazole.

MECHANISM	Inhibit fungal sterol (ergosterol) synthesis by inhibiting the cytochrome P-450 enzyme that converts lanosterol to ergosterol.
CLINICAL USE	Local and less serious systemic mycoses. Fluconazole for chronic suppression of cryptococcal meningitis in AIDS patients and candidal infections of all types. Itraconazole for *Blastomyces*, *Coccidioides*, *Histoplasma*. Clotrimazole and miconazole for topical fungal infections. Voriconazole for *Aspergillus* and some *Candida*. Isavuconazole for serious *Aspergillus* and Mucorales infections.
ADVERSE EFFECTS	Testosterone synthesis inhibition (gynecomastia, especially with ketoconazole), liver dysfunction (inhibits cytochrome P-450).

Terbinafine

MECHANISM	Inhibits the fungal enzyme squalene epoxidase.
CLINICAL USE	Dermatophytoses (especially onychomycosis—fungal infection of finger or toe nails).
ADVERSE EFFECTS	GI upset, headaches, hepatotoxicity, taste disturbance.

Echinocandins	Anidulafungin, caspofungin, micafungin.
MECHANISM	Inhibit cell wall synthesis by inhibiting synthesis of β-glucan.
CLINICAL USE	Invasive aspergillosis, *Candida*.
ADVERSE EFFECTS	GI upset, flushing (by histamine release).

Griseofulvin	
MECHANISM	Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (eg, nails).
CLINICAL USE	Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).
ADVERSE EFFECTS	Teratogenic, carcinogenic, confusion, headaches, disulfiram-like reaction, ↑ cytochrome P-450 and warfarin metabolism.

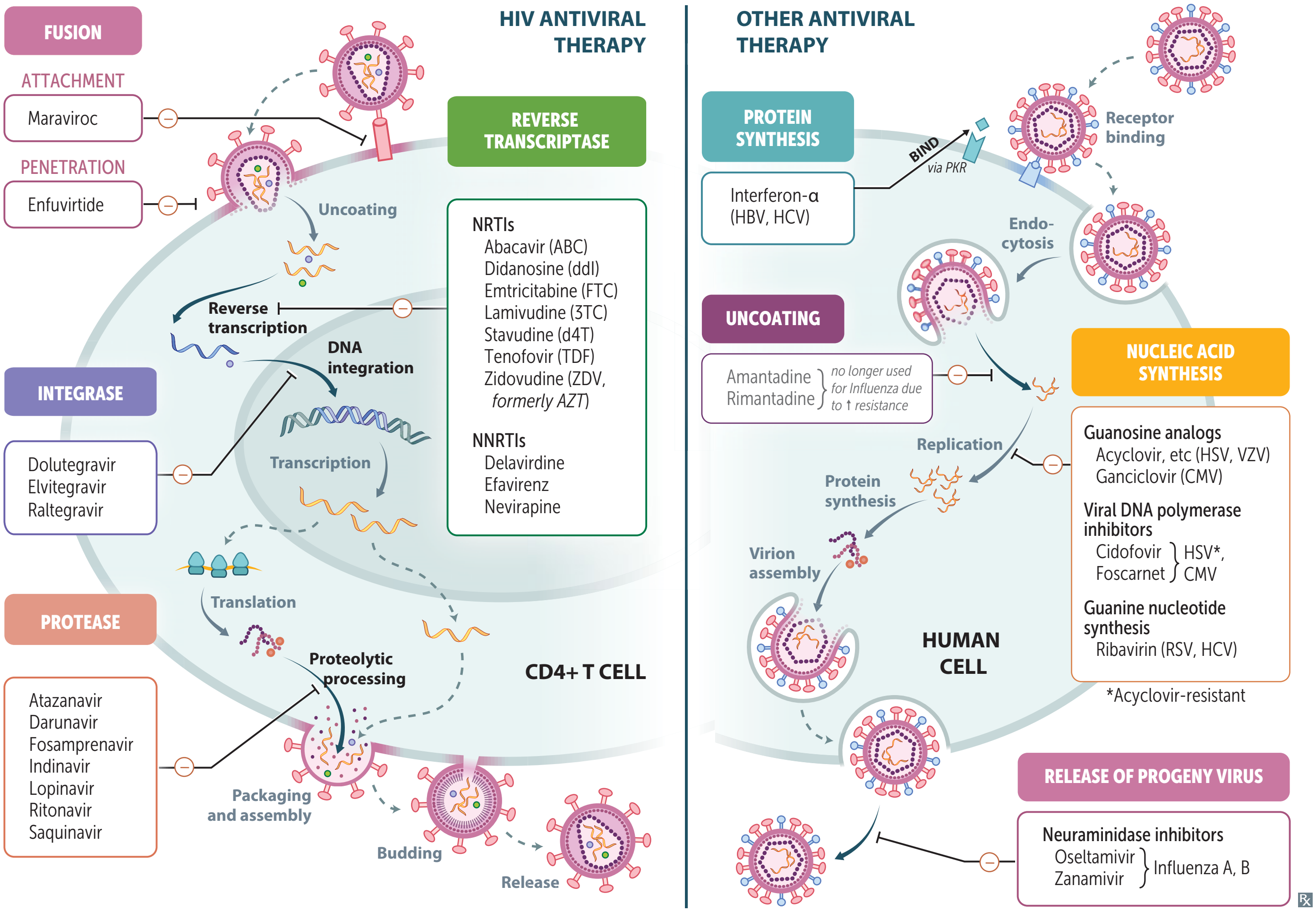
Antiprotozoan therapy	Pyrimethamine (toxoplasmosis), suramin and melarsoprol (*Trypanosoma brucei*), nifurtimox (*T cruzi*), sodium stibogluconate (leishmaniasis).

Anti-mite/louse therapy	Permethrin (neuronal membrane depolarization via Na^+ channels), malathion (acetylcholinesterase inhibitor), lindane (blocks GABA channels → neurotoxicity). Used to treat scabies (*Sarcoptes scabiei*) and lice (*Pediculus* and *Pthirus*).	Treat **PML** (**P**esty **M**ites and **L**ice) with **PML** (**P**ermethrin, **M**alathion, **L**indane), because they **NAG** you (**N**a, **A**ChE, **G**ABA blockade).

Chloroquine	
MECHANISM	Blocks detoxification of heme into hemozoin. Heme accumulates and is toxic to plasmodia.
CLINICAL USE	Treatment of plasmodial species other than *P falciparum* (frequency of resistance in *P falciparum* is too high). Resistance due to membrane pump that ↓ intracellular concentration of drug. Treat *P falciparum* with artemether/lumefantrine or atovaquone/proguanil. For life-threatening malaria, use quinidine in US (quinine elsewhere) or artesunate.
ADVERSE EFFECTS	Retinopathy; pruritus (especially in dark-skinned individuals).

Antihelminthic therapy	Mebendazole (microtubule inhibitor), pyrantel pamoate, ivermectin, diethylcarbamazine, praziquantel.

Antiviral therapy


HIV ANTIVIRAL THERAPY
FUSION
ATTACHMENT
Maraviroc
PENETRATION
Enfuvirtide
Uncoating
REVERSE TRANSCRIPTASE
NRTIs
Abacavir (ABC)
Didanosine (ddI)
Emtricitabine (FTC)
Lamivudine (3TC)
Stavudine (d4T)
Tenofovir (TDF)
Zidovudine (ZDV, formerly AZT)
NNRTIs
Delavirdine
Efavirenz
Nevirapine
Reverse transcription
DNA integration
INTEGRASE
Dolutegravir
Elvitegravir
Raltegravir
Transcription
Translation
PROTEASE
Atazanavir
Darunavir
Fosamprenavir
Indinavir
Lopinavir
Ritonavir
Saquinavir
Proteolytic processing
CD4+ T CELL
Packaging and assembly
Budding
Release
OTHER ANTIVIRAL THERAPY
PROTEIN SYNTHESIS
Interferon-α (HBV, HCV)
BIND via PKR
Receptor binding
Endocytosis
UNCOATING
Amantadine
Rimantadine
no longer used for Influenza due to ↑ resistance
NUCLEIC ACID SYNTHESIS
Guanosine analogs
Acyclovir, etc (HSV, VZV)
Ganciclovir (CMV)
Viral DNA polymerase inhibitors
Cidofovir
Foscarnet
HSV*, CMV
Guanine nucleotide synthesis
Ribavirin (RSV, HCV)
*Acyclovir-resistant
Replication
Protein synthesis
Virion assembly
HUMAN CELL
RELEASE OF PROGENY VIRUS
Neuraminidase inhibitors
Oseltamivir
Zanamivir
Influenza A, B

Oseltamivir, zanamivir

MECHANISM	Inhibit influenza neuraminidase → ↓ release of progeny virus.
CLINICAL USE	Treatment and prevention of both influenza A and B. Beginning therapy within 48 hours of symptom onset may shorten duration of illness.

Acyclovir, famciclovir, valacyclovir

MECHANISM	Guanosine analogs. Monophosphorylated by HSV/VZV thymidine kinase and not phosphorylated in uninfected cells → few adverse effects. Triphosphate formed by cellular enzymes. Preferentially inhibit viral DNA polymerase by chain termination.
CLINICAL USE	HSV and VZV. Weak activity against EBV. No activity against CMV. Used for HSV-induced mucocutaneous and genital lesions as well as for encephalitis. Prophylaxis in immunocompromised patients. No effect on latent forms of HSV and VZV. Valacyclovir, a prodrug of acyclovir, has better oral bioavailability. For herpes zoster, use famciclovir.
ADVERSE EFFECTS	Obstructive crystalline nephropathy and acute renal failure if not adequately hydrated.
MECHANISM OF RESISTANCE	Mutated viral thymidine kinase.

Ganciclovir

MECHANISM	5′-monophosphate formed by a CMV viral kinase. Guanosine analog. Triphosphate formed by cellular kinases. Preferentially inhibits viral DNA polymerase.
CLINICAL USE	CMV, especially in immunocompromised patients. Valganciclovir, a prodrug of ganciclovir, has better oral bioavailability.
ADVERSE EFFECTS	Bone marrow suppression (leukopenia, neutropenia, thrombocytopenia), renal toxicity. More toxic to host enzymes than acyclovir.
MECHANISM OF RESISTANCE	Mutated viral kinase.

Foscarnet

MECHANISM	Viral DNA/RNA polymerase inhibitor and HIV reverse transcriptase inhibitor. Binds to pyrophosphate-binding site of enzyme. Does not require any kinase activation.	**Fos**carnet = pyro**fos**phate analog.
CLINICAL USE	CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV.	
ADVERSE EFFECTS	Nephrotoxicity, electrolyte abnormalities (hypo- or hypercalcemia, hypo- or hyperphosphatemia, hypokalemia, hypomagnesemia) can lead to seizures.	
MECHANISM OF RESISTANCE	Mutated DNA polymerase.	

Cidofovir

MECHANISM	Preferentially inhibits viral DNA polymerase. Does not require phosphorylation by viral kinase.
CLINICAL USE	CMV retinitis in immunocompromised patients; acyclovir-resistant HSV. Long half-life.
ADVERSE EFFECTS	Nephrotoxicity (coadminister with probenecid and IV saline to ↓ toxicity).

HIV therapy

Highly active antiretroviral therapy (HAART): often initiated at the time of HIV diagnosis. Strongest indication for patients presenting with AIDS-defining illness, low CD4+ cell counts (< 500 cells/mm^3), or high viral load. Regimen consists of 3 drugs to prevent resistance: 2 NRTIs and preferably an integrase inhibitor.

DRUG	MECHANISM	TOXICITY
NRTIs		
Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC) Lamivudine (3TC) Stavudine (d4T) Tenofovir (TDF) Zidovudine (ZDV, formerly AZT)	Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain (lack a 3′ OH group). **T**enofovir is a nucleo**T**ide; the others are nucleosides. All need to be phosphorylated to be active. ZDV can be used for general prophylaxis and during pregnancy to ↓ risk of fetal transmission. Ha**ve you dined (vudine)** with my **nuclear** (**nucleo**sides) family?	Bone marrow suppression (can be reversed with granulocyte colony-stimulating factor [G-CSF] and erythropoietin), peripheral neuropathy, lactic acidosis (nucleosides), anemia (ZDV), pancreatitis (didanosine). Abacavir contraindicated if patient has HLA-B*5701 mutation due to ↑ risk of hypersensitivity.
NNRTIs		
Delavirdine Efavirenz Nevirapine	Bind to reverse transcriptase at site different from NRTIs. Do not require phosphorylation to be active or compete with nucleotides.	Rash and hepatotoxicity are common to all NNRTIs. Vivid dreams and CNS symptoms are common with efavirenz. Delavirdine and efavirenz are contraindicated in pregnancy.
Protease inhibitors		
Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir Ritonavir Saquinavir	Assembly of virions depends on HIV-1 protease (*pol* gene), which cleaves the polypeptide products of HIV mRNA into their functional parts. Thus, protease inhibitors prevent maturation of new viruses. Ritonavir can “boost” other drug concentrations by inhibiting cytochrome P-450. **Navir** (never) **tease** a **protease**.	Hyperglycemia, GI intolerance (nausea, diarrhea), lipodystrophy (Cushing-like syndrome). Nephropathy, hematuria, thrombocytopenia (indinavir). Rifampin (potent CYP/UGT inducer) reduces protease inhibitor concentrations; use rifabutin instead.
Integrase inhibitors		
Raltegravir Elvitegravir Dolutegravir	Inhibits HIV genome integration into host cell chromosome by reversibly inhibiting HIV integrase.	↑ creatine kinase.
Fusion inhibitors		
Enfuvirtide	Binds gp41, inhibiting viral entry.	Skin reaction at injection sites. Enf**u**virtide inhibits **fu**sion.
Maraviroc	Binds CCR-5 on surface of T cells/monocytes, inhibiting interaction with gp120.	Maravir**oc** inhibits d**oc**king.

Interferons

MECHANISM	Glycoproteins normally synthesized by virus-infected cells, exhibiting a wide range of antiviral and antitumoral properties.
CLINICAL USE	IFN-α: chronic hepatitis B and C, Kaposi sarcoma, hairy cell leukemia, condyloma acuminatum, renal cell carcinoma, malignant melanoma. IFN-β: multiple sclerosis. IFN-γ: chronic granulomatous disease.
ADVERSE EFFECTS	Flu-like symptoms, depression, neutropenia, myopathy.

Hepatitis C therapy

DRUG	MECHANISM	CLINICAL USE
Ribavirin	Inhibits synthesis of guanine nucleotides by competitively inhibiting inosine monophosphate dehydrogenase.	Chronic HCV; also used in RSV (palivizumab preferred in children) Adverse effects: hemolytic anemia; severe teratogen.
Sofosbuvir	Inhibits HCV RNA-dependent RNA polymerase acting as a chain terminator.	Chronic HCV in combination with ribavirin, simeprevir, ledipasvir (NS5A inhibitor), +/– peginterferon alfa. Do not use as monotherapy. Adverse effects: fatigue, headache, nausea.
Simeprevir	HCV protease inhibitor; prevents viral replication.	Chronic HCV in combination with ledipasvir (NS5A inhibitor). Do not use as monotherapy. Adverse effects: photosensitivity reactions, rash.

Disinfection and sterilization	Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the inactivation of self-propagating biological entities (sterilization).
Autoclave	Pressurized steam at > 120°C. May be sporicidal.
Alcohols	Denature proteins and disrupt cell membranes. Not sporicidal.
Chlorhexidine	Denatures proteins and disrupts cell membranes. Not sporicidal.
Hydrogen peroxide	Free radical oxidation. Sporicidal.
Iodine and iodophors	Halogenation of DNA, RNA, and proteins. May be sporicidal.

Antimicrobials to avoid in pregnancy

ANTIMICROBIAL	ADVERSE EFFECT
Sulfonamides	Kernicterus
Aminoglycosides	Ototoxicity
Fluoroquinolones	Cartilage damage
Clarithromycin	Embryotoxic
Tetracyclines	Discolored teeth, inhibition of bone growth
Ribavirin	Teratogenic
Griseofulvin	Teratogenic
Chloramphenicol	Gray baby syndrome

SAFe **C**hildren **T**ake **R**eally **G**ood **C**are.

NOTES

HIGH-YIELD PRINCIPLES IN

Pathology

"Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology."

—Friedrich Nietzsche

"You cannot separate passion from pathology any more than you can separate a person's spirit from his body."

—Richard Selzer

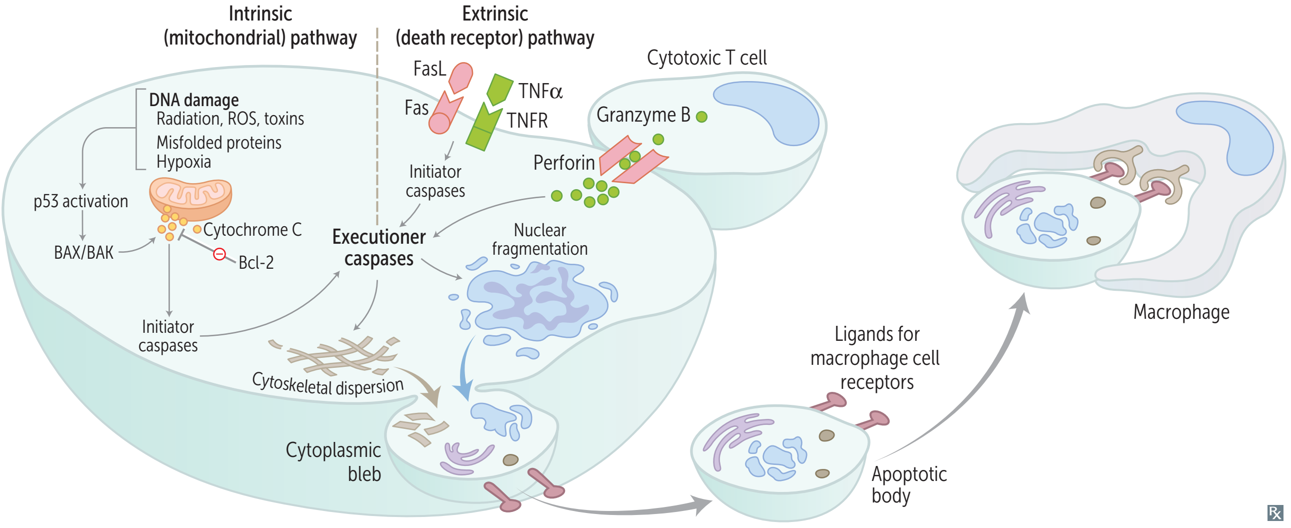
The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions across different organ systems, and such topics are definitely high yield. For example, the concepts of cell injury and inflammation are key to understanding the inflammatory response that follows myocardial infarction, a very common subject of board questions. Similarly, a familiarity with the early cellular changes that culminate in the development of neoplasias—for example, esophageal or colon cancer—is critical. Finally, make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts such as tumor staging and metastasis.

▸ Inflammation 204

▸ Neoplasia 214

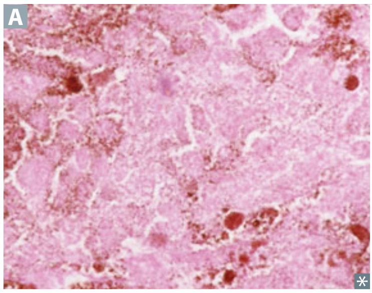
▶ PATHOLOGY—INFLAMMATION

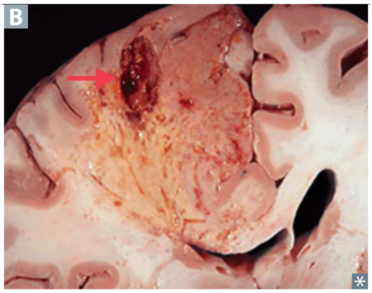
Apoptosis	ATP-dependent programmed cell death. Intrinsic and extrinsic pathways; both pathways activate caspases (cytosolic proteases) → cellular breakdown including cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed. Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis (nuclear shrinkage), and karyorrhexis (fragmentation caused by endonuclease-mediated cleavage). Cell membrane typically remains intact without significant inflammation (unlike necrosis). DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.
Intrinsic (mitochondrial) pathway	Involved in tissue remodeling in embryogenesis. Occurs when a regulating factor is withdrawn from a proliferating cell population (eg, ↓ IL-2 after a completed immunologic reaction → apoptosis of proliferating effector cells). Also occurs after exposure to injurious stimuli (eg, radiation, toxins, hypoxia). Regulated by Bcl-2 family of proteins. BAX and BAK are proapoptotic, while Bcl-2 and Bcl-x are antiapoptotic. Bcl-2 keeps the mitochondrial outer membrane impermeable and therefore prevents cytochrome c release from the inner mitochondrial matrix. Bcl-2 overexpression (eg, follicular lymphoma t[14;18]) → ↓ caspase activation → tumorigenesis.
Extrinsic (death receptor) pathway	2 pathways: ▪ Ligand receptor interactions (FasL binding to Fas [CD95] or TNF-α binding to its receptor) ▪ Immune cell (cytotoxic T-cell release of perforin and granzyme B) Fas-FasL interaction is necessary in thymic medullary negative selection. Mutations in Fas ↑ numbers of circulating self-reacting lymphocytes due to failure of clonal deletion. Defective Fas-FasL interactions cause autoimmune lymphoproliferative syndrome.

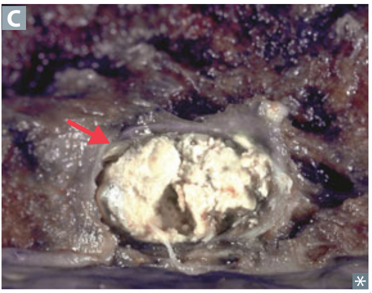

Intrinsic (mitochondrial) pathway
Extrinsic (death receptor) pathway
FasL
Fas
TNFα
TNFR
Cytotoxic T cell
Granzyme B
Perforin
DNA damage
Radiation, ROS, toxins
Misfolded proteins
Hypoxia
p53 activation
BAX/BAK
Cytochrome C
Bcl-2
Initiator caspases
Initiator caspases
Executioner caspases
Nuclear fragmentation
Cytoskeletal dispersion
Cytoplasmic bleb
Ligands for macrophage cell receptors
Apoptotic body
Macrophage

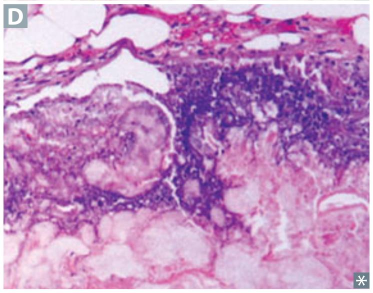
Necrosis Enzymatic degradation and protein denaturation of cell due to exogenous injury → intracellular components leak. Inflammatory process (unlike apoptosis).

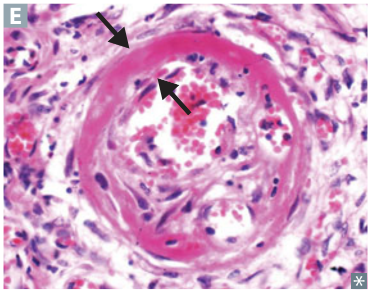
TYPE	SEEN IN	DUE TO	HISTOLOGY
Coagulative	Ischemia/infarcts in most tissues (except brain)	Ischemia or infarction; proteins denature, then enzymatic degradation	Cell outlines preserved but nuclei disappear; ↑ cytoplasmic binding of eosin dyes A
Liquefactive	Bacterial abscesses, brain infarcts	Neutrophils release lysosomal enzymes that digest the tissue B; enzymatic degradation first, then proteins denature	Early: cellular debris and macrophages Late: cystic spaces and cavitation (brain) Neutrophils and cell debris seen with bacterial infection
Caseous	TB, systemic fungi (eg, *Histoplasma capsulatum*), *Nocardia*	Macrophages wall off the infecting microorganism → granular debris C	Fragmented cells and debris surrounded by lymphocytes and macrophages
Fat	Enzymatic: acute pancreatitis (saponification of peripancreatic fat) Nonenzymatic: traumatic (eg, injury to breast tissue)	Damaged cells release lipase to break down triglycerides, liberating fatty acids to bind calcium → saponification	Outlines of dead fat cells without peripheral nuclei; saponification of fat (combined with Ca^{2+}) appears dark blue on H&E stain D
Fibrinoid	Immune reactions in vessels (eg, polyarteritis nodosa), preeclampsia, malignant hypertension	Immune complexes combine with fibrin → vessel wall damage (type III hypersensitivity reaction)	Vessel walls are thick and pink E
Gangrenous	Distal extremity and GI tract, after chronic ischemia	Dry: ischemia F	Coagulative
		Wet: superinfection	Liquefactive superimposed on coagulative

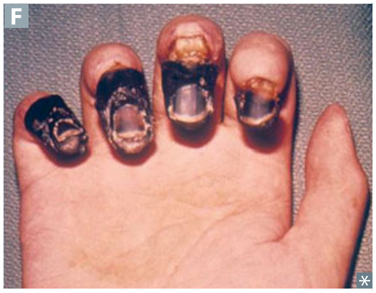




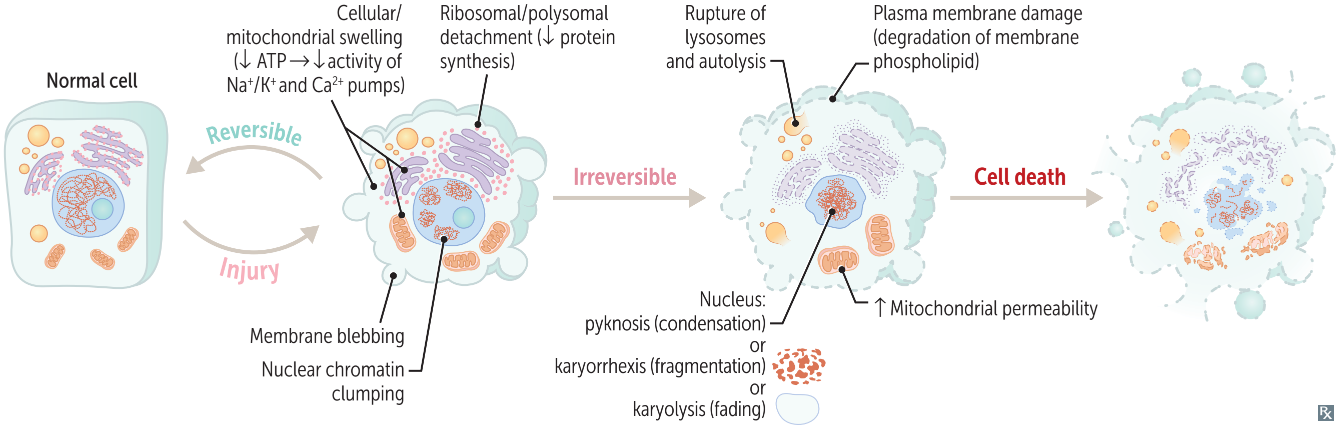




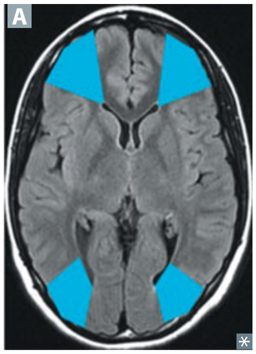




Cell injury


Normal cell
Reversible
Injury
Cellular/ mitochondrial swelling (↓ ATP → ↓ activity of Na+/K+ and Ca2+ pumps)
Ribosomal/polysomal detachment (↓ protein synthesis)
Membrane blebbing
Nuclear chromatin clumping
Irreversible
Rupture of lysosomes and autolysis
Plasma membrane damage (degradation of membrane phospholipid)
Nucleus:
pyknosis (condensation)
or
karyorrhexis (fragmentation)
or
karyolysis (fading)
↑ Mitochondrial permeability
Cell death

Ischemia



Inadequate blood supply to meet demand.

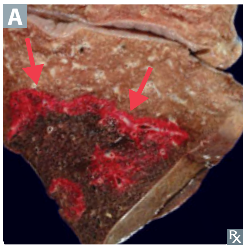
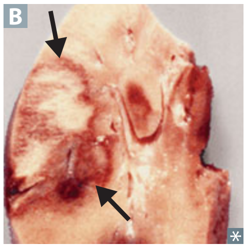
Regions most vulnerable to hypoxia/ischemia and subsequent infarction:

ORGAN	REGION
Brain	ACA/MCA/PCA boundary areas[a,b]
Heart	Subendocardium (LV)
Kidney	Straight segment of proximal tubule (medulla) Thick ascending limb (medulla)
Liver	Area around central vein (zone III)
Colon	Splenic flexure,[a] rectum[a]

[a] Watershed areas (border zones) receive blood supply from most distal branches of 2 arteries with limited collateral vascularity. These areas are susceptible to ischemia from hypoperfusion (eg, ACA/MCA [anterior] and MCA/PCA [posterior] watershed areas in blue A).

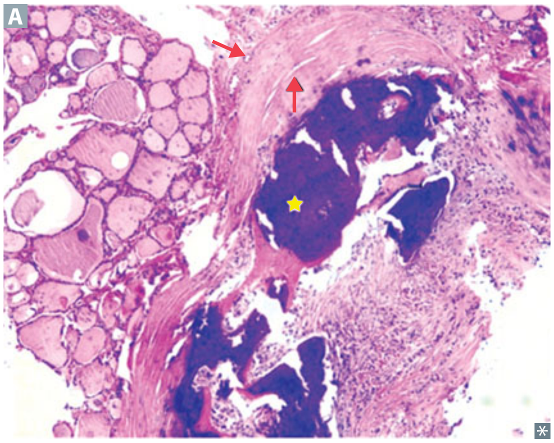
[b] Neurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex (zones 3, 5, 6).

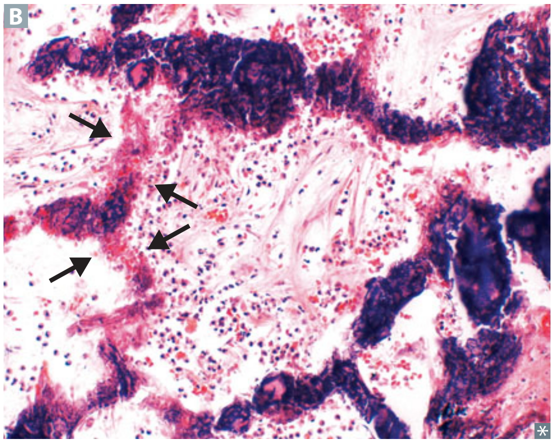
Types of infarcts

Red infarct 	Red (hemorrhagic) infarcts A occur in venous occlusion and tissues with multiple blood supplies, such as liver, lung, intestine, testes; reperfusion (eg, after angioplasty). Reperfusion injury is due to damage by free radicals. Red = reperfusion.
Pale infarct 	Pale (anemic) infarcts B occur in solid organs with a single (end-arterial) blood supply, such as heart, kidney, and spleen.

Inflammation	Characterized by *rubor* (redness), *dolor* (pain), *calor* (heat), *tumor* (swelling), and *functio laesa* (loss of function).
Vascular component	↑ vascular permeability, vasodilation, endothelial injury.
Cellular component	Neutrophils extravasate from circulation to injured tissue to participate in inflammation through phagocytosis, degranulation, and inflammatory mediator release.
Acute	Neutrophil, eosinophil, antibody (pre-existing), mast cell, and basophil mediated. Acute inflammation is rapid onset (seconds to minutes) and of short duration (minutes to days). Outcomes include complete resolution, abscess formation, or progression to chronic inflammation.
Chronic	Mononuclear cell (monocytes/macrophages, lymphocytes, plasma cells) and fibroblast mediated. Characterized by persistent destruction and repair. Associated with blood vessel proliferation, fibrosis. Granuloma: nodular collections of epithelioid macrophages and giant cells. Outcomes include scarring, amyloidosis, and neoplastic transformation.

Types of calcification	Dystrophic calcification	Metastatic calcification
CA^{2+} DEPOSITION	In abnormal tissues	In normal tissues
EXTENT	Tends to be localized (eg, calcific aortic stenosis) **A** shows dystrophic calcification (yellow star), and thick fibrotic wall (red arrows)	Widespread (ie, diffuse, metastatic) **B** shows metastatic calcifications of alveolar walls in acute pneumonitis (arrows)
ASSOCIATED CONDITIONS	TB (lung and pericardium) and other granulomatous infections; liquefactive necrosis of chronic abscesses; fat necrosis; infarcts; thrombi; schistosomiasis; congenital CMV, toxoplasmosis, rubella; psammoma bodies; CREST syndrome	Predominantly in interstitial tissues of kidney, lung, and gastric mucosa (these tissues lose acid quickly; ↑ pH favors Ca^{2+} deposition) Nephrocalcinosis of collecting ducts may lead to nephrogenic diabetes insipidus and renal failure
ETIOLOGY	2° to injury or necrosis	2° to hypercalcemia (eg, 1° hyperparathyroidism, sarcoidosis, hypervitaminosis D) or high calcium-phosphate product levels (eg, chronic renal failure with 2° hyperparathyroidism, long-term dialysis, calciphylaxis, multiple myeloma)
SERUM CA^{2+} LEVELS	Patients are usually normocalcemic	Patients are usually not normocalcemic

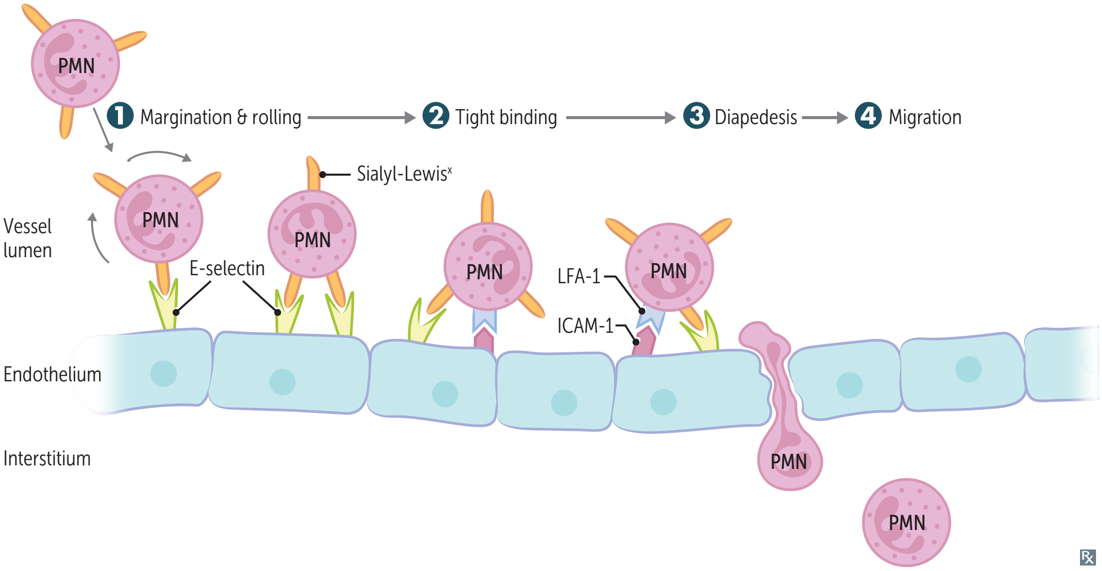




Leukocyte extravasation

Extravasation predominantly occurs at postcapillary venules.
WBCs exit from blood vessels at sites of tissue injury and inflammation in 4 steps:

STEP	VASCULATURE/STROMA	LEUKOCYTE
① Margination and rolling—defective in leukocyte adhesion deficiency type 2 (↓ Sialyl-Lewis^X)	E-selectin (upregulated by TNF and IL-1) P-selectin (released from Weibel-Palade bodies) GlyCAM-1, CD34	Sialyl-Lewis^X Sialyl-Lewis^X L-selectin
② Tight binding (adhesion)—defective in leukocyte adhesion deficiency type 1 (↓ CD18 integrin subunit)	ICAM-1 (CD54) VCAM-1 (CD106)	CD11/18 integrins (LFA-1, Mac-1) VLA-4 integrin
③ Diapedesis—WBC travels between endothelial cells and exits blood vessel	PECAM-1 (CD31)	PECAM-1 (CD31)
④ Migration—WBC travels through interstitium to site of injury or infection guided by chemotactic signals	Chemotactic products released in response to bacteria: C5a, IL-8, LTB$_4$, kallikrein, platelet-activating factor	Various


PMN
① Margination & rolling
② Tight binding
③ Diapedesis
④ Migration
Sialyl-Lewis^x
Vessel lumen
PMN
PMN
E-selectin
PMN
LFA-1
ICAM-1
PMN
Endothelium
Interstitium
PMN
PMN

Free radical injury

Free radicals damage cells via membrane lipid peroxidation, protein modification, and DNA breakage.

Initiated via radiation exposure (eg, cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide (eg, inflammation), transition metals, WBC (eg, neutrophils, macrophages) oxidative burst.

Free radicals can be eliminated by scavenging enzymes (eg, catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (eg, vitamins A, C, E), and certain metal carrier proteins (eg, transferrin, ceruloplasmin).

Examples:

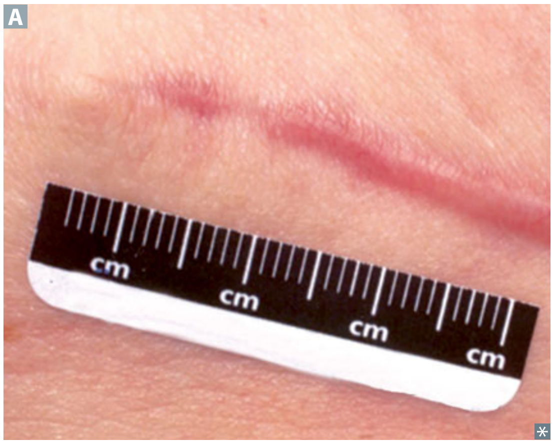
- Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia, reperfusion injury after thrombolytic therapy
- Drug/chemical toxicity: carbon tetrachloride and acetaminophen overdose (hepatotoxicity)
- Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

Scar formation

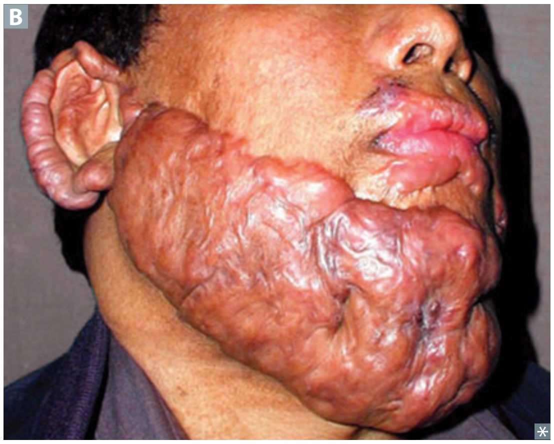
70–80% of tensile strength regained at 3 months; minimal additional tensile strength will be regained afterward.

SCAR TYPE	**Hypertrophic** A	**Keloid** B
COLLAGEN SYNTHESIS	↑ (type III collagen)	↑↑↑ (disorganized types I and III collagen)
COLLAGEN ORGANIZATION	Parallel	Disorganized
EXTENT OF SCAR	Confined to borders of original wound	Extends beyond borders of original wound with “claw-like” projections typically on earlobes, face, upper extremities
RECURRENCE	Infrequent	Frequent
PREDISPOSITION	None	↑ incidence in ethnic groups with darker skin

A



B



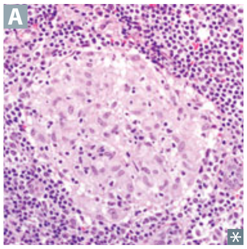
Wound healing

Tissue mediators

MEDIATOR	ROLE
PDGF	Secreted by activated platelets and macrophages Induces vascular remodeling and smooth muscle cell migration Stimulates fibroblast growth for collagen synthesis
FGF	Stimulates angiogenesis
EGF	Stimulates cell growth via tyrosine kinases (eg, EGFR/*ErbB1*)
TGF-β	Angiogenesis, fibrosis
Metalloproteinases	Tissue remodeling
VEGF	Stimulates angiogenesis

PHASE OF WOUND HEALING	EFFECTOR CELLS	CHARACTERISTICS
Inflammatory (up to 3 days after wound)	Platelets, neutrophils, macrophages	Clot formation, ↑ vessel permeability and neutrophil migration into tissue; macrophages clear debris 2 days later
Proliferative (day 3–weeks after wound)	Fibroblasts, myofibroblasts, endothelial cells, keratinocytes, macrophages	Deposition of granulation tissue and type III collagen, angiogenesis, epithelial cell proliferation, dissolution of clot, and wound contraction (mediated by myofibroblasts) Delayed wound healing in vitamin C deficiency and copper deficiency
Remodeling (1 week–6+ months after wound)	Fibroblasts	Type III collagen replaced by type I collagen, ↑ tensile strength of tissue Delayed wound healing in zinc deficiency

Granulomatous diseases



Bacterial:
- *Mycobacteria* (tuberculosis, leprosy)
- *Bartonella henselae* (cat scratch disease)
- *Listeria monocytogenes* (granulomatosis infantiseptica)
- *Treponema pallidum* (3° syphilis)

Fungal: endemic mycoses (eg, histoplasmosis)

Parasitic: schistosomiasis

Chronic granulomatous disease

Autoinflammatory:
- Sarcoidosis
- Crohn disease
- Primary biliary cirrhosis
- Subacute (de Quervain/granulomatous) thyroiditis
- Granulomatosis with polyangiitis (Wegener)
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- Giant cell (temporal) arteritis
- Takayasu arteritis

Foreign material: berylliosis, talcosis, hypersensitivity pneumonitis

Granulomas are composed of epithelioid cells (macrophages with abundant pink cytoplasm) with surrounding multinucleated giant cells and lymphocytes. Th_1 cells secrete IFN-γ, activating macrophages. TNF-α from macrophages induces and maintains granuloma formation. Anti-TNF drugs can, as a side effect, cause sequestering granulomas to break down, leading to disseminated disease. Always test for latent TB before starting anti-TNF therapy.

Associated with hypercalcemia due to calcitriol (1,25-$[OH]_2$ vitamin D_3) production.

Caseating necrosis is more common with an infectious etiology (eg, TB). Diagnosis of sarcoidosis requires noncaseating granulomas **A** on biopsy.

Exudate vs transudate

Exudate	Transudate
Cellular (cloudy)	Hypocellular (clear)
↑ protein (> 2.9 g/dL) ↑ LDH (vs serum)	↓ protein (< 2.5 g/dL) ↓ LDH (vs serum)
Due to: ▪ Lymphatic obstruction (chylous) ▪ Inflammation/infection ▪ Malignancy	Due to: ▪ ↑ hydrostatic pressure (eg, HF, Na^+ retention) ▪ ↓ oncotic pressure (eg, cirrhosis, nephrotic syndrome)

Light criteria

Diagnostic analysis comparing serum and pleural fluid protein and LDH levels.

Pleural effusion is exudative if ≥ 1 of the following criteria is met:

- Pleural effusion protein/serum protein ratio > 0.5
- Pleural effusion LDH/serum LDH ratio > 0.6
- Pleural effusion LDH > ⅔ of the upper limit of normal for serum LDH

Erythrocyte sedimentation rate

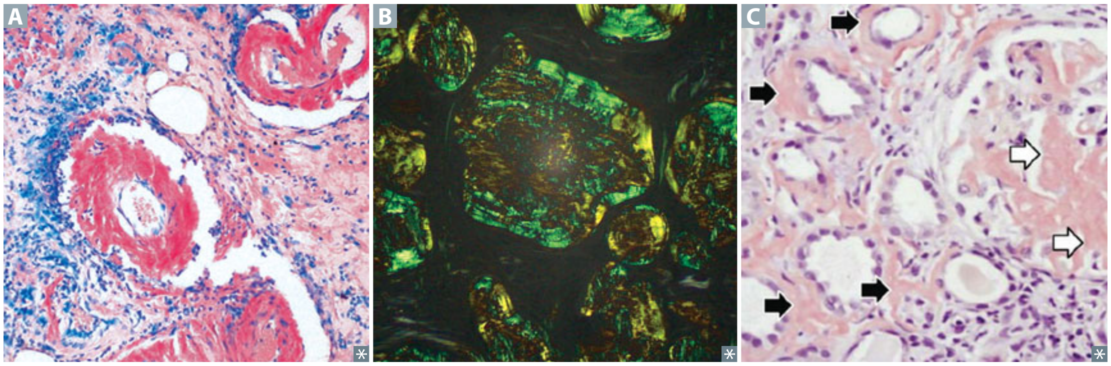
Products of inflammation (eg, fibrinogen) coat RBCs and cause aggregation. The denser RBC aggregates fall at a faster rate within a pipette tube. Often co-tested with CRP levels.

↑ ESR	↓ ESR
Most anemias	Sickle cell anemia (altered shape)
Infections	Polycythemia (↑ RBCs "dilute" aggregation factors)
Inflammation (eg, giant cell [temporal] arteritis, polymyalgia rheumatica)	HF
Cancer (eg, metastases, multiple myeloma)	Microcytosis
Renal disease (end-stage or nephrotic syndrome)	Hypofibrinogenemia
Pregnancy	

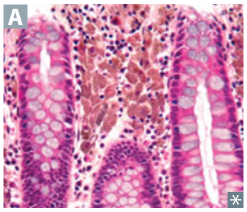
Amyloidosis

Abnormal aggregation of proteins (or their fragments) into β-pleated linear sheets → insoluble fibrils → cellular damage and apoptosis. Amyloid deposits visualized by Congo red stain A, polarized light (apple green birefringence) B, and H&E stain (C shows deposits in glomerular mesangial areas [white arrows], tubular basement membranes [black arrows]).

COMMON TYPES	DESCRIPTION
AL (primary)	Due to deposition of proteins from Ig Light chains. Can occur as a plasma cell disorder or associated with multiple myeloma. Often affects multiple organ systems, including renal (nephrotic syndrome), cardiac (restrictive cardiomyopathy, arrhythmia), hematologic (easy bruising, splenomegaly), GI (hepatomegaly), and neurologic (neuropathy).
AA (secondary)	Seen with chronic inflammatory conditions such as rheumatoid arthritis, IBD, spondyloarthropathy, familial Mediterranean fever, protracted infection. Fibrils composed of serum Amyloid A. Often multisystem like AL amyloidosis.
Dialysis-related	Fibrils composed of β_2-microglobulin in patients with ESRD and/or on long-term dialysis. May present as carpal tunnel syndrome.
Heritable	Heterogeneous group of disorders, including familial amyloid polyneuropathies due to transthyretin gene mutation.
Age-related (senile) systemic	Due to deposition of normal (wild-type) transthyretin (TTR) predominantly in cardiac ventricles. Slower progression of cardiac dysfunction relative to AL amyloidosis.
Organ-specific	Amyloid deposition localized to a single organ. Most important form is amyloidosis in Alzheimer disease due to deposition of β-amyloid protein cleaved from amyloid precursor protein (APP). Islet amyloid polypeptide (IAPP) is commonly seen in diabetes mellitus type 2 and is caused by deposition of amylin in pancreatic islets. Isolated atrial amyloidosis due to atrial natriuretic peptide is common in normal aging and can predispose to increased risk of atrial fibrillation. Amyloid deposition to ventricular endomyocardium in restrictive cardiomyopathy. Calcitonin deposition in tumor cells in medullary carcinoma of the thyroid.



Lipofuscin



A yellow-brown "wear and tear" pigment A associated with normal aging.

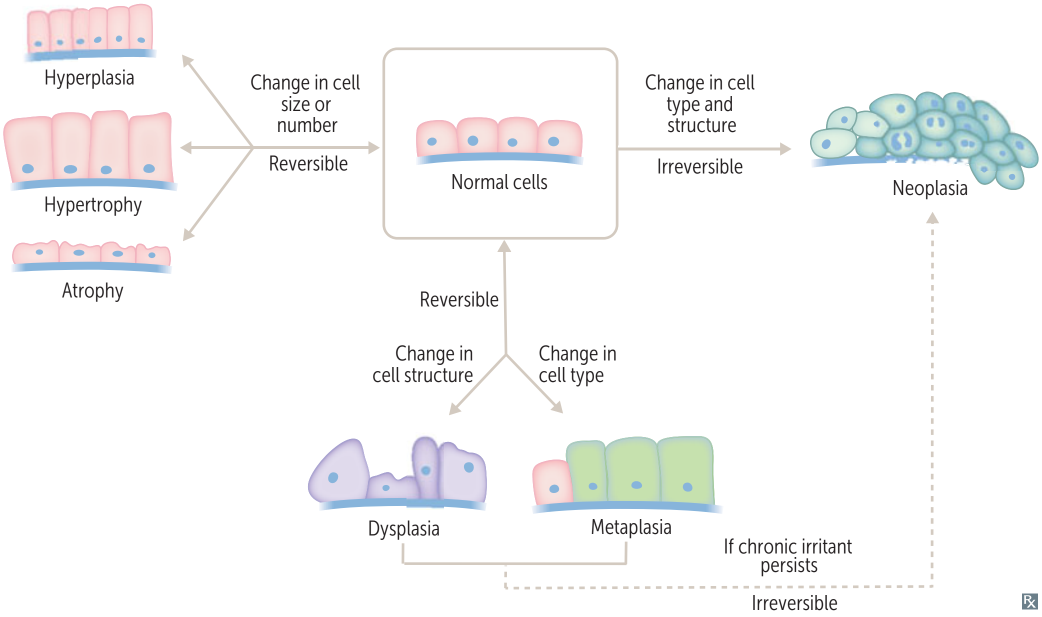
Formed by oxidation and polymerization of autophagocytosed organellar membranes.

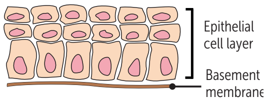
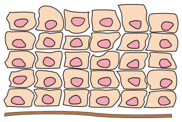
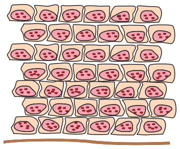
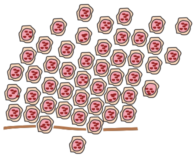
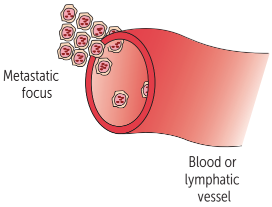
Autopsy of elderly person will reveal deposits in heart, colon, liver, kidney, eye, and other organs.

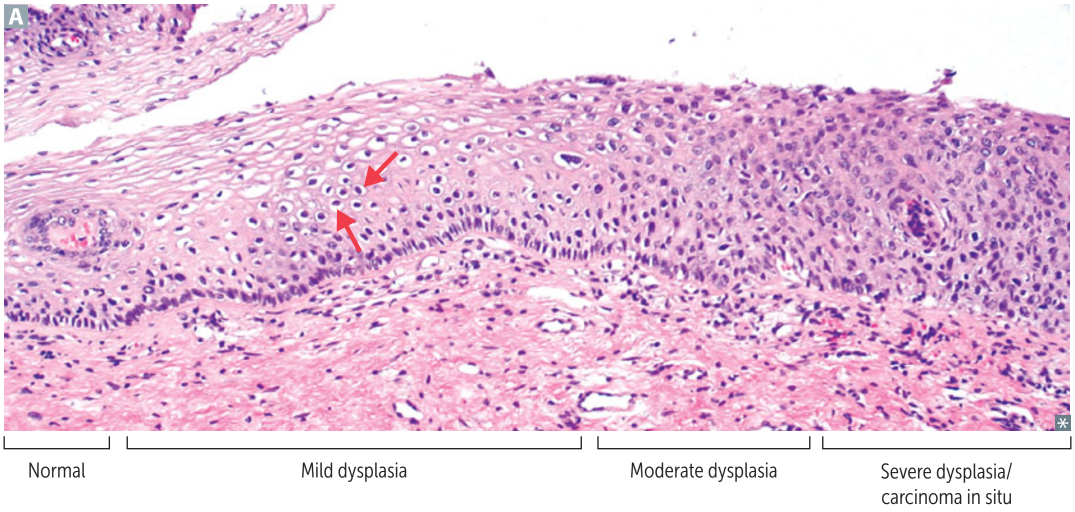
▸ PATHOLOGY—NEOPLASIA

Cellular changes

Hyperplasia	↑ in number of cells. May be a risk factor for future malignancy (eg, endometrial hyperplasia) but not considered premalignant.
Hypertrophy	↑ in size of cells.
Atrophy	↓ in tissue mass due to ↓ in size and/or number of cells. Causes include disuse, denervation, loss of blood supply, loss of hormonal stimulation, poor nutrition.
Dysplasia	Disordered, non-neoplastic cell growth. Term used only with epithelial cells. Mild dysplasia is usually reversible; severe dysplasia usually progresses to carcinoma in situ.
Metaplasia	Replacement of one cell type by another. Usually due to exposure to an irritant, such as gastric acid or cigarette smoke. Reversible if the irritant is removed but may undergo malignant transformation with persistent insult (eg, Barrett esophagus → esophageal adenocarcinoma).
Neoplasia	Uncontrolled, clonal proliferation of cells. Can be benign or malignant.
Anaplasia	Complete lack of differentiation of cells in a malignant neoplasm.
Differentiation	The degree to which a malignant tumor resembles its tissue of origin: ▪ Well-differentiated tumors (often less aggressive) closely resemble their tissue of origin. ▪ Poorly differentiated tumors (often more aggressive) look almost nothing like their tissue of origin.


Hyperplasia
Hypertrophy
Atrophy
Change in cell size or number
Reversible
Normal cells
Change in cell type and structure
Irreversible
Neoplasia
Reversible
Change in cell structure
Change in cell type
Dysplasia
Metaplasia
If chronic irritant persists
Irreversible

Neoplastic progression	Hallmarks of cancer: evasion of apoptosis, growth signal self-sufficiency, anti-growth signal insensitivity, sustained angiogenesis, limitless replicative potential, tissue invasion, and metastasis.
Normal cells  Epithelial cell layer Basement membrane	Normal cells with basal → apical polarity. See cervical example A, which shows normal cells and spectrum of dysplasia, as discussed below.
Dysplasia 	Abnormal proliferation of cells with loss of size, shape, and orientation (eg, koilocytic change, arrow in A). Compare vs hyperplasia (cells ↑ in number).
Carcinoma in situ/ preinvasive 	Neoplastic cells have not invaded the intact basement membrane. ↑ nuclear:cytoplasmic ratio and clumped chromatin. Neoplastic cells encompass entire thickness.
Invasive carcinoma 	Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases). Cell-cell contacts lost by inactivation of E-cadherin.
Metastasis  Metastatic focus Blood or lymphatic vessel	Spread to distant organ via lymphatics or blood. “Seed and soil” theory of metastasis: ▪ Seed = tumor embolus. ▪ Soil = target organ is often the first-encountered capillary bed (eg, liver, lungs, bone, brain, etc).


A
Normal
Mild dysplasia
Moderate dysplasia
Severe dysplasia/ carcinoma in situ

Tumor grade vs stage

Grade	Degree of cellular differentiation and mitotic activity on histology. Range from low grade (well differentiated) to high grade (poorly differentiated, undifferentiated or anaplastic).	Stage generally has more prognostic value than grade (eg, a high-stage yet low-grade tumor is usually worse than a low-stage yet high-grade tumor).
Stage	Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases. Based on clinical (c) or pathology (p) findings. Example: cT3N1M0	TNM staging system (**S**tage = **S**pread): **T** = **T**umor size/invasiveness **N** = **N**ode involvement **M** = **M**etastases Each TNM factor has independent prognostic value; N and M factors are often most important.

Tumor nomenclature

Carcinoma implies epithelial origin, whereas **sarcoma** denotes mesenchymal origin. Both terms imply malignancy.

Benign tumors are usually well differentiated, well demarcated, low mitotic activity, no metastasis, no necrosis.

Malignant tumors may show poor differentiation, erratic growth, local invasion, metastasis, and ↓ apoptosis. Upregulation of telomerase prevents chromosome shortening and cell death.

Terms for non-neoplastic malformations include hamartoma (disorganized overgrowth of tissues in their native location, eg, Peutz-Jeghers polyps) and choristoma (normal tissue in a foreign location, eg, gastric tissue located in distal ileum in Meckel diverticulum).

CELL TYPE	BENIGN	MALIGNANT
Epithelium	Adenoma, papilloma	Adenocarcinoma, papillary carcinoma
Mesenchyme		
Blood cells		Leukemia, lymphoma
Blood vessels	Hemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
Connective tissue	Fibroma	Fibrosarcoma
Bone	Osteoma	Osteosarcoma
Fat	Lipoma	Liposarcoma
Melanocyte	Nevus/mole	Melanoma

Cancer epidemiology

Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included below).

	MEN	WOMEN	CHILDREN (AGE 0–14)	NOTES
Cancer incidence	1. Prostate 2. Lung 3. Colon/rectum	1. Breast 2. Lung 3. Colon/rectum	1. Leukemia 2. Brain and CNS 3. Neuroblastoma	Lung cancer incidence has dropped in men, but has not changed significantly in women.
Cancer mortality	1. Lung 2. Prostate 3. Colon/rectum	1. Lung 2. Breast 3. Colon/rectum	1. Leukemia 2. Brain and CNS 3. Neuroblastoma	Cancer is the 2nd leading cause of death in the United States (heart disease is 1st).

Paraneoplastic syndromes

MANIFESTATION	DESCRIPTION/MECHANISM	MOST COMMONLY ASSOCIATED CANCER(S)
Cutaneous		
Acanthosis nigricans	Hyperpigmented velvety plaques in axilla and neck	Gastric adenocarcinoma and other visceral malignancies (but more commonly associated with obesity and insulin resistance)
Sign of Leser-Trélat	Sudden onset of multiple seborrheic keratoses	GI adenocarcinomas and other visceral malignancies
Endocrine		
Hypercalcemia	PTHrP	Squamous cell carcinomas of lung, head, and neck; renal, bladder, breast, and ovarian carcinomas
	↑ 1,25-$(OH)_2$ vitamin D_3 (calcitriol)	Lymphoma
Cushing syndrome	↑ ACTH	Small cell lung cancer
Hyponatremia (SIADH)	↑ ADH	
Hematologic		
Polycythemia	↑ Erythropoietin	Renal cell carcinoma, hepatocellular carcinoma, hemangioblastoma, pheochromocytoma, leiomyoma
Pure red cell aplasia	Anemia with low reticulocytes	Thymoma
Good syndrome	Hypogammaglobulinemia	
Trousseau syndrome	Migratory superficial thrombophlebitis	Adenocarcinomas, especially pancreatic
Nonbacterial thrombotic (marantic) endocarditis	Deposition of sterile platelet thrombi on heart valves	
Neuromuscular		
Anti-NMDA receptor encephalitis	Psychiatric disturbance, memory deficits, seizures, dyskinesias, autonomic instability, language dysfunction	Ovarian teratoma
Opsoclonus-myoclonus ataxia syndrome	"Dancing eyes, dancing feet"	Neuroblastoma (children), small cell lung cancer (adults)
Paraneoplastic cerebellar degeneration	Antibodies against antigens in Purkinje cells	Small cell lung cancer (anti-Hu), gynecologic and breast cancers (anti-Yo), and Hodgkin lymphoma (anti-Tr)
Paraneoplastic encephalomyelitis	Antibodies against Hu antigens in neurons	Small cell lung cancer
Lambert-Eaton myasthenic syndrome	Antibodies against presynaptic (P/Q-type) Ca^{2+} channels at NMJ	Small cell lung cancer
Myasthenia gravis	Antibodies against postsynaptic ACh receptors at NMJ	Thymoma

Oncogenes Gain of function → ↑ cancer risk. Need damage to only one allele of an oncogene.

GENE	GENE PRODUCT	ASSOCIATED NEOPLASM
ALK	Receptor tyrosine kinase	Lung adenocarcinoma
BCR-ABL	Tyrosine kinase	CML, ALL
BCL-2	Antiapoptotic molecule (inhibits apoptosis)	Follicular and diffuse large B cell lymphomas
BRAF	Serine/threonine kinase	Melanoma, non-Hodgkin lymphoma, papillary thyroid carcinoma
c-KIT	Cytokine receptor	Gastrointestinal stromal tumor (GIST)
c-MYC	Transcription factor	Burkitt lymphoma
HER2/neu (c-erbB2)	Receptor tyrosine kinase	Breast and gastric carcinomas
JAK2	Tyrosine kinase	Chronic myeloproliferative disorders
KRAS	GTPase	Colon cancer, lung cancer, pancreatic cancer
MYCL1	Transcription factor	Lung tumor
MYCN	Transcription factor	Neuroblastoma
RET	Receptor tyrosine kinase	MEN 2A and 2B, medullary thyroid cancer

Tumor suppressor genes Loss of function → ↑ cancer risk; both (two) alleles of a tumor suppressor gene must be lost for expression of disease.

GENE	GENE PRODUCT	ASSOCIATED CONDITION
APC	Negative regulator of β-catenin/WNT pathway	Colorectal cancer (associated with FAP)
BRCA1/BRCA2	DNA repair protein	Breast, ovarian, and pancreatic cancer
CDKN2A	p16, blocks G_1 → S phase	Melanoma, pancreatic cancer
DCC	DCC—Deleted in Colon Cancer	Colon cancer
DPC4/SMAD4	DPC—Deleted in Pancreatic Cancer	Pancreatic cancer
MEN1	Menin	MEN 1
NF1	Neurofibromin (Ras GTPase activating protein)	Neurofibromatosis type 1
NF2	Merlin (schwannomin) protein	Neurofibromatosis type 2
PTEN	Tyrosine phosphatase of PIP_3 (eg, protein kinase B [AKT] activation)	Breast cancer, prostate cancer, endometrial cancer
Rb	Inhibits E2F; blocks G_1 → S phase	Retinoblastoma, osteosarcoma
TP53	*p53*, activates p21, blocks G_1 → S phase	Most human cancers, Li-Fraumeni syndrome (multiple malignancies at early age, aka, SBLA cancer syndrome: Sarcoma, Breast, Leukemia, Adrenal gland)
TSC1	Hamartin protein	Tuberous sclerosis
TSC2	Tuberin protein	Tuberous sclerosis
VHL	Inhibits hypoxia inducible factor 1a	von Hippel-Lindau disease
WT1	Transcription factor that regulates urogenital development	Wilms tumor (nephroblastoma)

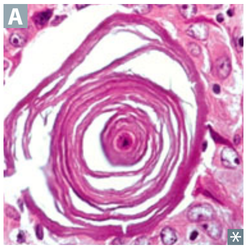
Oncogenic microbes

Microbe	Associated cancer
EBV	Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1° CNS lymphoma (in immunocompromised patients)
HBV, HCV	Hepatocellular carcinoma
HHV-8	Kaposi sarcoma
HPV	Cervical and penile/anal carcinoma (types 16, 18), head and neck cancer
H pylori	Gastric adenocarcinoma and MALT lymphoma
HTLV-1	Adult T-cell leukemia/lymphoma
Liver fluke (*Clonorchis sinensis*)	Cholangiocarcinoma
Schistosoma haematobium	Bladder cancer (squamous cell)

Carcinogens

TOXIN	ORGAN	IMPACT
Aflatoxins (*Aspergillus*)	Liver	Hepatocellular carcinoma
Alkylating agents	Blood	Leukemia/lymphoma
Aromatic amines (eg, benzidine, 2-naphthylamine)	Bladder	Transitional cell carcinoma
Arsenic	Liver Lung Skin	Angiosarcoma Lung cancer Squamous cell carcinoma
Asbestos	Lung	Bronchogenic carcinoma > mesothelioma
Carbon tetrachloride	Liver	Centrilobular necrosis, fatty change
Cigarette smoke	Bladder Cervix Esophagus Kidney Larynx Lung Pancreas	Transitional cell carcinoma Cervical carcinoma Squamous cell carcinoma/adenocarcinoma Renal cell carcinoma Squamous cell carcinoma Squamous cell and small cell carcinoma Pancreatic adenocarcinoma
Ethanol	Esophagus Liver	Squamous cell carcinoma Hepatocellular carcinoma
Ionizing radiation	Thyroid	Papillary thyroid carcinoma
Nitrosamines (smoked foods)	Stomach	Gastric cancer
Radon	Lung	Lung cancer (2nd leading cause after cigarette smoke)
Vinyl chloride	Liver	Angiosarcoma

Psammoma bodies



Laminated, concentric spherules with dystrophic calcification A, PSaMMoma bodies are seen in:

- Papillary carcinoma of thyroid
- Serous papillary cystadenocarcinoma of ovary
- Meningioma
- Malignant Mesothelioma

Serum tumor markers

Tumor markers should not be used as the 1° tool for cancer diagnosis or screening. They may be used to monitor tumor recurrence and response to therapy, but definitive diagnosis is made via biopsy.

MARKER	ASSOCIATED CANCER	NOTES
Alkaline phosphatase	Metastases to bone or liver, Paget disease of bone, seminoma (placental ALP).	Must exclude hepatic origin by checking LFTs and GGT levels.
α-fetoprotein	Hepatocellular carcinoma, hepatoblastoma, yolk sac (endodermal sinus) tumor, mixed germ cell tumor.	Normally made by fetus. Transiently elevated in pregnancy. High levels associated with neural tube and abdominal wall defects, low levels associated with Down syndrome.
β-hCG	Hydatidiform moles and Choriocarcinomas (Gestational trophoblastic disease), testicular cancer, mixed germ cell tumor.	Produced by syncytiotrophoblasts of the placenta.
CA 15-3/CA 27-29	Breast cancer.	
CA 19-9	Pancreatic adenocarcinoma.	
CA 125	Ovarian cancer.	
Calcitonin	Medullary thyroid carcinoma (alone and in MEN2A, MEN2B).	
CEA	Major associations: colorectal and pancreatic cancers. Minor associations: gastric, breast, and medullary thyroid carcinomas.	Carcinoembryonic antigen. Very nonspecific.
Chromogranin	Neuroendocrine tumors.	
PSA	Prostate cancer.	Prostate-specific antigen. Can also be elevated in BPH and prostatitis. Questionable risk/benefit for screening. Surveillance marker for recurrent disease after prostatectomy.

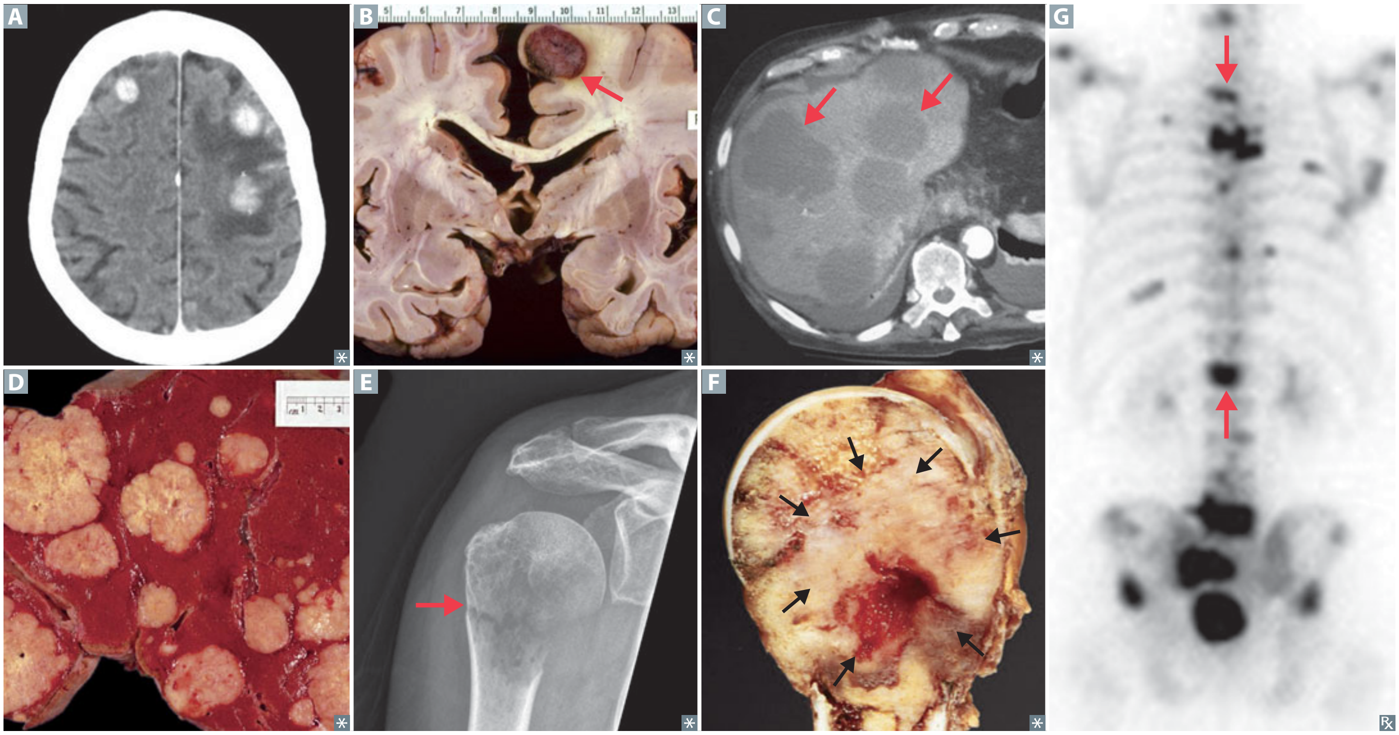
P-glycoprotein

Also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenocortical carcinoma but also expressed by other cancer cells (eg, colon, liver). Used to pump out toxins, including chemotherapeutic agents (one mechanism of ↓ responsiveness or resistance to chemotherapy over time).

Cachexia Weight loss, muscle atrophy, and fatigue that occur in chronic disease (eg, cancer, AIDS, heart failure, COPD). Mediated by TNF, IFN-γ, IL-1, and IL-6.

Common metastases Most sarcomas spread hematogenously; most carcinomas spread via lymphatics. However, **F**our **C**arcinomas **R**oute **H**ematogenously: **F**ollicular thyroid carcinoma, **C**horiocarcinoma, **R**enal cell carcinoma, and **H**epatocellular carcinoma.

SITE OF METASTASIS	1° TUMOR	NOTES
Brain	Lung > breast > melanoma, colon, kidney.	50% of brain tumors are from metastases A B. Commonly seen as multiple well-circumscribed tumors at gray/white matter junction.
Liver	Colon >> stomach > pancreas.	Liver C D and lung are the most common sites of metastasis after the regional lymph nodes.
Bone	Prostate, breast > lung, thyroid, kidney.	Bone metastasis E F >> 1° bone tumors (eg, multiple myeloma, lytic). Common mets to bone: breast (mixed), lung (lytic), thyroid (lytic), kidney (lytic), prostate (blastic). Predilection for axial skeleton G.



NOTES

HIGH-YIELD PRINCIPLES IN

Pharmacology

"Take me, I am the drug; take me, I am hallucinogenic."
—Salvador Dali

"I was under medication when I made the decision not to burn the tapes."
—Richard Nixon

"I wondher why ye can always read a doctor's bill an' ye niver can read his purscription."
—Finley Peter Dunne

"Once you get locked into a serious drug collection, the tendency is to push it as far as you can."
—Hunter S. Thompson

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (eg, mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the "classic" and distinguishing toxicities of the major drugs. Specific drug dosages or trade names are generally not testable. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs. Much of the material is clinically relevant. We occasionally mention drugs that are no longer available in the US, but help illustrate high-yield pharmacologic or disease mechanisms. They are highlighted as being of historical significance and should not appear on the USMLE. However, recently approved drugs are fair game for the exam.

▸ Pharmacokinetics & Pharmacodynamics 224
▸ Autonomic Drugs 229
▸ Toxicities and Side Effects 239
▸ Miscellaneous 244

▸ PHARMACOLOGY—PHARMACOKINETICS & PHARMACODYNAMICS

Enzyme kinetics

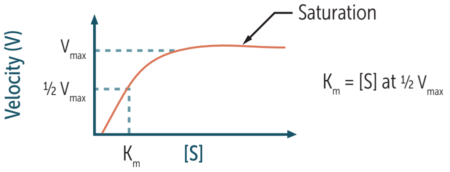
Michaelis-Menten kinetics

K_m is inversely related to the affinity of the enzyme for its substrate.

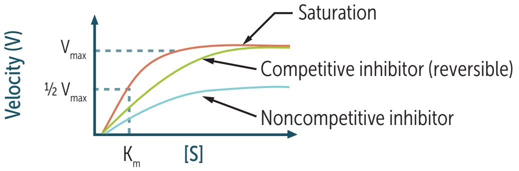
V_{max} is directly proportional to the enzyme concentration.

Most enzymatic reactions follow a hyperbolic curve (ie, Michaelis-Menten kinetics); however, enzymatic reactions that exhibit a sigmoid curve usually indicate cooperative kinetics (eg, hemoglobin).

[S] = concentration of substrate; V = velocity.



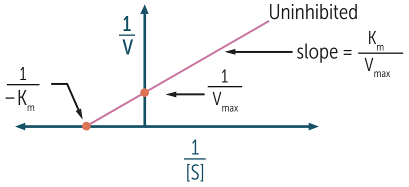
Effects of enzyme inhibition



Lineweaver-Burk plot

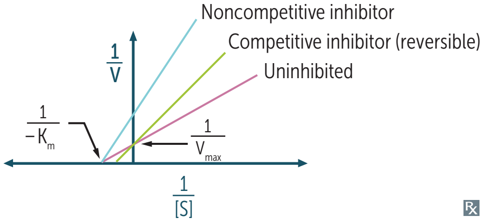
↑ y-intercept, ↓ V_{max}.

The further to the right the x-intercept (ie, closer to zero), the greater the K_m and the lower the affinity.



Reversible competitive inhibitors cross each other competitively, whereas noncompetitive inhibitors do not.

Effects of enzyme inhibition



	Competitive inhibitors, reversible	Competitive inhibitors, irreversible	Noncompetitive inhibitors
Resemble substrate	Yes	Yes	No
Overcome by ↑ [S]	Yes	No	No
Bind active site	Yes	Yes	No
Effect on V_{max}	Unchanged	↓	↓
Effect on K_m	↑	Unchanged	Unchanged
Pharmacodynamics	↓ potency	↓ efficacy	↓ efficacy

Pharmacokinetics

Bioavailability (F)

Fraction of administered drug reaching systemic circulation unchanged. For an IV dose, F = 100%. Orally: F typically < 100% due to incomplete absorption and first-pass metabolism.

Volume of distribution (V_d)

Theoretical volume occupied by the total amount of drug in the body relative to its plasma concentration. Apparent V_d of plasma protein–bound drugs can be altered by liver and kidney disease (↓ protein binding, ↑ V_d). Drugs may distribute in more than one compartment.

$$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$$

V_d	COMPARTMENT	DRUG TYPES
Low	Intravascular	Large/charged molecules; plasma protein bound
Medium	ECF	Small hydrophilic molecules
High	All tissues including fat	Small lipophilic molecules, especially if bound to tissue protein

Clearance (CL)

The volume of plasma cleared of drug per unit time. Clearance may be impaired with defects in cardiac, hepatic, or renal function.

$$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e \text{ (elimination constant)}$$

Half-life ($t_{1/2}$)

The time required to change the amount of drug in the body by ½ during elimination.

In first-order kinetics, a drug infused at a constant rate takes 4–5 half-lives to reach steady state. It takes 3.3 half-lives to reach 90% of the steady-state level.

$$t_{1/2} = \frac{0.693 \times V_d}{CL} \text{ in first-order elimination}$$

# of half-lives	1	2	3	4
% remaining	50%	25%	12.5%	6.25%

Dosage calculations

$$\text{Loading dose} = \frac{C_p \times V_d}{F}$$

$$\text{Maintenance dose} = \frac{C_p \times CL \times \tau}{F}$$

C_p = target plasma concentration at steady state
τ = dosage interval (time between doses), if not administered continuously

In renal or liver disease, maintenance dose ↓ and loading dose is usually unchanged.

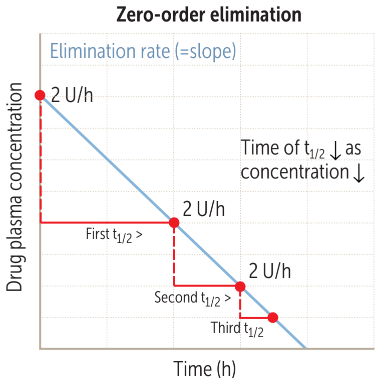
Time to steady state depends primarily on $t_{1/2}$ and is independent of dose and dosing frequency.

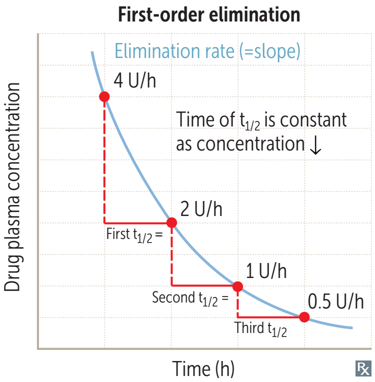
Types of drug interactions

TERM	DEFINITION	EXAMPLE
Additive	Effect of substance A and B together is equal to the sum of their individual effects	Aspirin and acetaminophen
Permissive	Presence of substance A is required for the full effects of substance B	Cortisol on catecholamine responsiveness
Synergistic	Effect of substance A and B together is greater than the sum of their individual effects	Clopidogrel with aspirin
Tachyphylactic	Acute decrease in response to a drug after initial/repeated administration	Nitrates, niacin, phenylephrine, LSD, MDMA

Elimination of drugs

Zero-order elimination	Rate of elimination is constant regardless of C_p (ie, constant **amount** of drug eliminated per unit time). C_p ↓ linearly with time. Examples of drugs—**P**henytoin, **E**thanol, and **A**spirin (at high or toxic concentrations).	Capacity-limited elimination. **PEA.** (A pea is round, shaped like the "**0**" in **zero**-order.)
First-order elimination	Rate of elimination is directly proportional to the drug concentration (ie, constant **fraction** of drug eliminated per unit time). C_p ↓ exponentially with time. Applies to most drugs.	Flow-dependent elimination.





Urine pH and drug elimination

Ionized species are trapped in urine and cleared quickly. Neutral forms can be reabsorbed.

Weak acids	Examples: phenobarbital, methotrexate, aspirin (salicylates). Trapped in basic environments. Treat overdose with bicarbonate to alkalinize urine. $\underset{\text{(lipid soluble)}}{RCOOH} \rightleftharpoons \underset{\text{(trapped)}}{RCOO^- + H^+}$
Weak bases	Example: amphetamines, TCAs. Trapped in acidic environments. Treat overdose with ammonium chloride to acidify urine. $\underset{\text{(trapped)}}{RNH_3^+} \rightleftharpoons \underset{\text{(lipid soluble)}}{RNH_2 + H^+}$

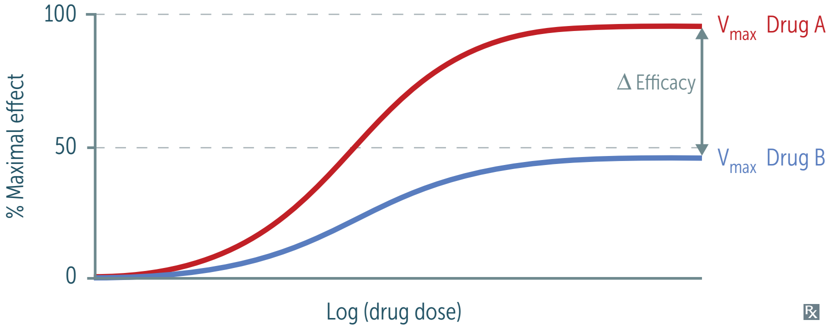
Drug metabolism

Phase I	Reduction, oxidation, hydrolysis with cytochrome P-450 usually yield slightly polar, water-soluble metabolites (often still active).	Geriatric patients lose phase I first.
Phase II	Conjugation (**M**ethylation, **G**lucuronidation, **A**cetylation, **S**ulfation) usually yields very polar, inactive metabolites (renally excreted).	Geriatric patients have **M**ore **GAS** (phase II). Patients who are slow acetylators have ↑ side effects from certain drugs because of ↓ rate of metabolism.

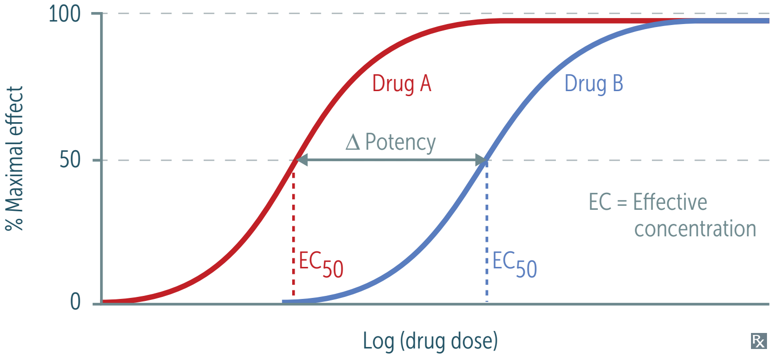
Efficacy vs potency

Efficacy	Maximal effect a drug can produce. Represented by the y-value (V_{max}). ↑ y-value = ↑ V_{max} = ↑ efficacy. Unrelated to potency (ie, efficacious drugs can have high or low potency). Partial agonists have less efficacy than full agonists.
Potency	Amount of drug needed for a given effect. Represented by the x-value (EC_{50}). Left shifting = ↓ EC_{50} = ↑ potency = ↓ drug needed. Unrelated to efficacy (ie, potent drugs can have high or low efficacy).

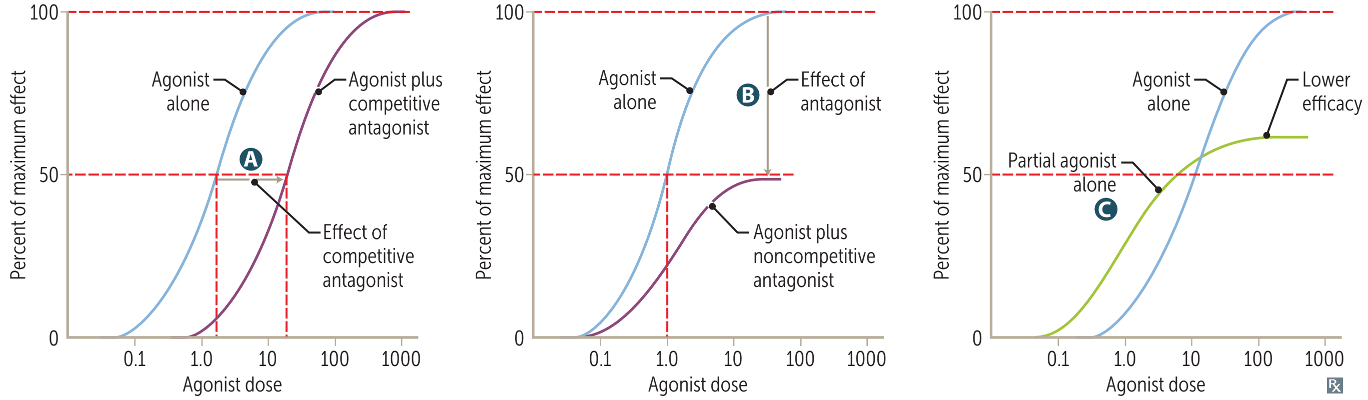
RELATIVE EFFICACY



RELATIVE POTENCY



Receptor binding



AGONIST WITH	EFFECT	EXAMPLE
Ⓐ Competitive antagonist	Shifts curve right (↓ potency), no change in efficacy. Can be overcome by ↑ the concentration of agonist substrate.	Diazepam (agonist) + **flumazenil** (competitive antagonist) on GABA receptor.
Ⓑ Noncompetitive antagonist	Shifts curve down (↓ efficacy). Cannot be overcome by ↑ agonist substrate concentration.	Norepinephrine (agonist) + **phenoxybenzamine** (noncompetitive antagonist) on α-receptors.
Ⓒ Partial agonist (alone)	Acts at same site as full agonist, but with lower maximal effect (↓ efficacy). Potency is an independent variable.	Morphine (full agonist) vs **buprenorphine** (partial agonist) at opioid μ-receptors.

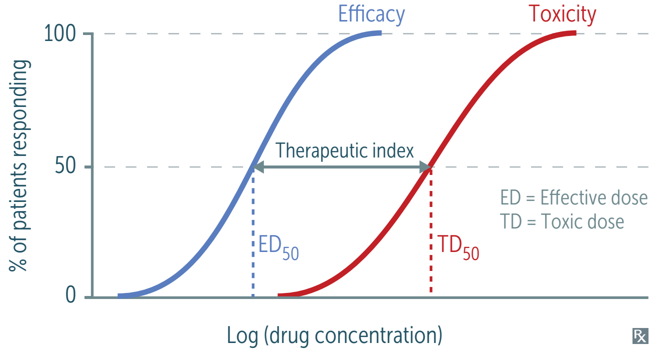
Therapeutic index

Measurement of drug safety.

$$\frac{TD_{50}}{ED_{50}} = \frac{\text{median toxic dose}}{\text{median effective dose}}$$

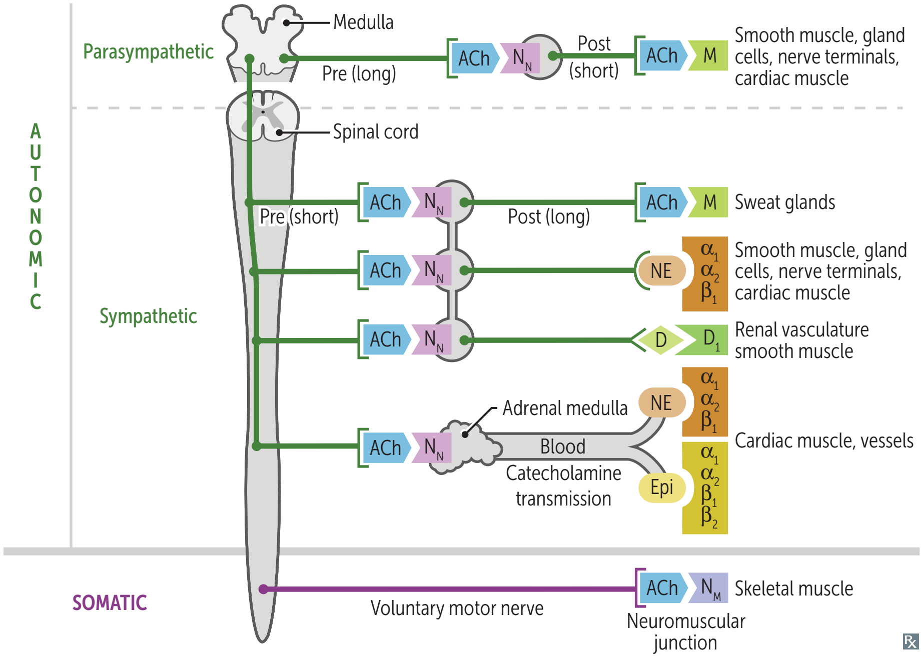
Therapeutic window—dosage range that can safely and effectively treat disease.

TITE: **T**herapeutic **I**ndex = **T**D$_{50}$ / **E**D$_{50}$.
Safer drugs have higher TI values. Drugs with lower TI values frequently require monitoring (eg, **W**arfarin, **T**heophylline, **D**igoxin, **L**ithium; **W**arning! **T**hese **D**rugs are **L**ethal!).
LD$_{50}$ (lethal median dose) often replaces TD$_{50}$ in animal studies.



▶ PHARMACOLOGY—AUTONOMIC DRUGS

Central and peripheral nervous system


AUTONOMIC
Parasympathetic
Medulla
Pre (long)
ACh
N_N
Post (short)
ACh
M
Smooth muscle, gland cells, nerve terminals, cardiac muscle
Spinal cord
Sympathetic
Pre (short)
ACh
N_N
Post (long)
ACh
M
Sweat glands
ACh
N_N
NE
α_1 α_2 β_1
Smooth muscle, gland cells, nerve terminals, cardiac muscle
ACh
N_N
D
D_1
Renal vasculature smooth muscle
Adrenal medulla
NE
α_1 α_2 β_1
ACh
N_N
Blood
Catecholamine transmission
Epi
α_1 α_2 β_1 β_2
Cardiac muscle, vessels
SOMATIC
Voluntary motor nerve
ACh
N_M
Skeletal muscle
Neuromuscular junction

Adrenal medulla is directly innervated by preganglionic sympathetic fibers.
Sweat glands are part of the sympathetic pathway but are innervated by cholinergic fibers.

Acetylcholine receptors

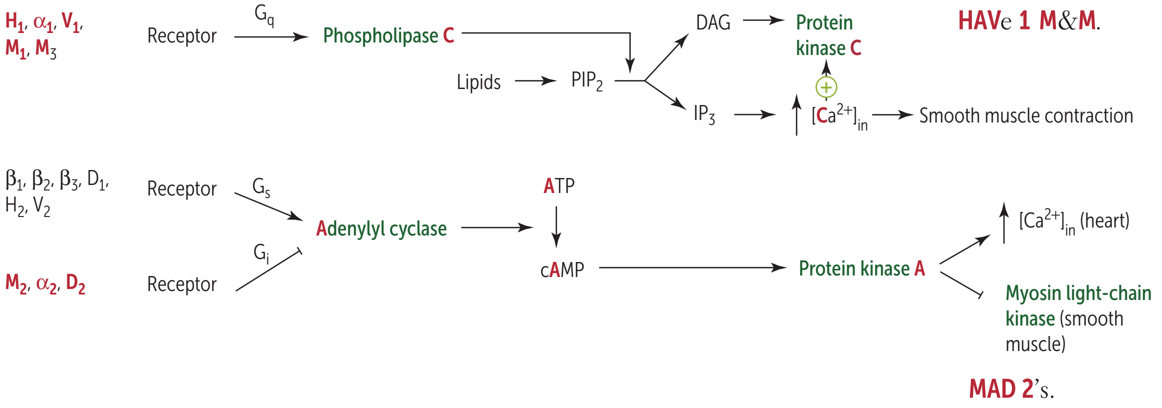
Nicotinic ACh receptors are ligand-gated Na^+/K^+ channels. Two subtypes: N_N (found in autonomic ganglia, adrenal medulla) and N_M (found in neuromuscular junction of skeletal muscle).

Muscarinic ACh receptors are G-protein–coupled receptors that usually act through 2nd messengers. 5 subtypes: $M_{1–5}$ found in heart, smooth muscle, brain, exocrine glands, and on sweat glands (cholinergic sympathetic).

G-protein–linked second messengers

RECEPTOR	G-PROTEIN CLASS	MAJOR FUNCTIONS
Sympathetic		
α_1	**q**	↑ vascular smooth muscle contraction, ↑ pupillary dilator muscle contraction (mydriasis), ↑ intestinal and bladder sphincter muscle contraction
α_2	**i**	↓ sympathetic (adrenergic) outflow, ↓ insulin release, ↓ lipolysis, ↑ platelet aggregation, ↓ aqueous humor production
β_1	**s**	↑ heart rate, ↑ contractility (**one** heart), ↑ renin release, ↑ lipolysis
β_2	**s**	Vasodilation, bronchodilation (**two** lungs), ↑ lipolysis, ↑ insulin release, ↓ uterine tone (tocolysis), ciliary muscle relaxation, ↑ aqueous humor production
β_3	**s**	↑ lipolysis, ↑ thermogenesis in skeletal muscle, ↑ bladder relaxation
Parasympathetic		
M_1	**q**	Mediates higher cognitive functions, stimulates enteric nervous system
M_2	**i**	↓ heart rate and contractility of atria
M_3	**q**	↑ exocrine gland secretions (eg, lacrimal, sweat, salivary, gastric acid), ↑ gut peristalsis, ↑ bladder contraction, bronchoconstriction, ↑ pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation), ↑ insulin release
Dopamine		
D_1	**s**	Relaxes renal vascular smooth muscle, activates direct pathway of striatum
D_2	**i**	Modulates transmitter release, especially in brain, inhibits indirect pathway of striatum
Histamine		
H_1	**q**	↑ nasal and bronchial mucus production, ↑ vascular permeability, contraction of bronchioles, pruritus, pain
H_2	**s**	↑ gastric acid secretion
Vasopressin		
V_1	**q**	↑ vascular smooth muscle contraction
V_2	**s**	↑ H_2O permeability and reabsorption in collecting **tu**bules of kidney

“After **qisses** (kisses), you get a **qiq** (kick) out of **siq** (sick) **sqs** (super qinky sex).”

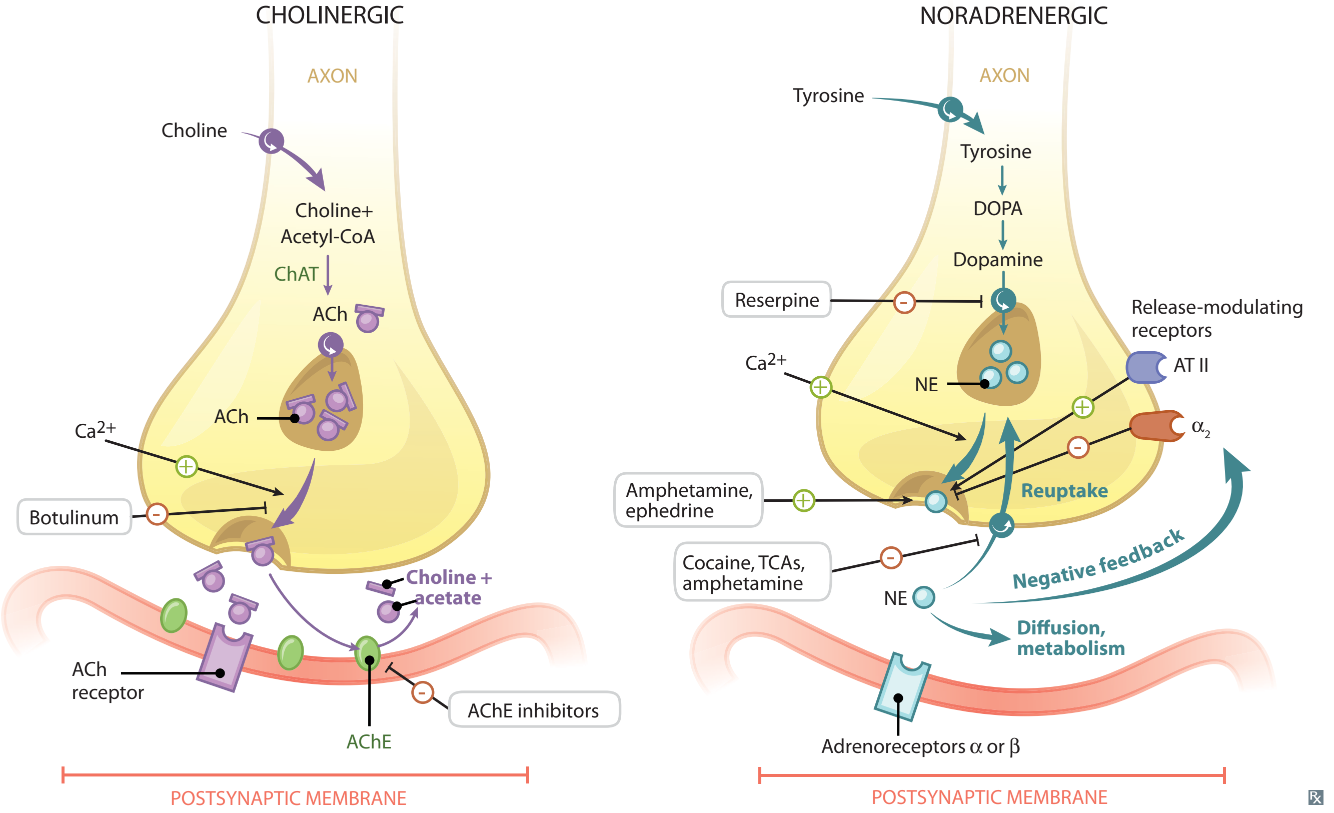


H1, α1, V1, M1, M3
Receptor
Gq
Phospholipase C
Lipids
PIP2
DAG
Protein kinase C
IP3
[Ca2+]in
Smooth muscle contraction
HAVe 1 M&M.
β1, β2, β3, D1, H2, V2
Receptor
Gs
M2, α2, D2
Receptor
Gi
Adenylyl cyclase
ATP
cAMP
Protein kinase A
[Ca2+]in (heart)
Myosin light-chain kinase (smooth muscle)
MAD 2’s.

Autonomic drugs

Release of norepinephrine from a sympathetic nerve ending is modulated by NE itself, acting on presynaptic α_2-autoreceptors → negative feedback.

Amphetamines use the NE transporter (NET) to enter the presynaptic terminal, where they utilize the vesicular monoamine transporter (VMAT) to enter neurosecretory vesicles. This displaces NE from the vesicles. Once NE reaches a concentration threshold within the presynaptic terminal, the action of NET is reversed, and NE is expelled into the synaptic cleft, contributing to the characteristics and effects of ↑ NE observed in patients taking amphetamines.


CHOLINERGIC
AXON
Choline
Choline+
Acetyl-CoA
ChAT
ACh
ACh
Ca^{2+}
Botulinum
Choline +
acetate
ACh
receptor
AChE
AChE inhibitors
POSTSYNAPTIC MEMBRANE
NORADRENERGIC
AXON
Tyrosine
Tyrosine
DOPA
Dopamine
Reserpine
Release-modulating
receptors
AT II
Ca^{2+}
NE
α_2
Amphetamine,
ephedrine
Reuptake
Cocaine, TCAs,
amphetamine
NE
Negative feedback
Diffusion,
metabolism
Adrenoreceptors α or β
POSTSYNAPTIC MEMBRANE

Circles with rotating arrows represent transporters.

Cholinomimetic agents

DRUG	ACTION	APPLICATIONS
Direct agonists		
Bethanechol	Activates bowel and bladder smooth muscle; resistant to AChE, no nicotinic activity. "Bethany, call (bethanechol) me to activate your bowels and bladder."	Postoperative ileus, neurogenic ileus, urinary retention
Carbachol	Carbon copy of acetylcholine (but resistant to AChE).	Constricts pupil and relieves intraocular pressure in open-angle glaucoma
Methacholine	Stimulates muscarinic receptors in airway when inhaled.	Challenge test for diagnosis of asthma
Pilocarpine	Contracts ciliary muscle of eye (open-angle glaucoma), pupillary sphincter (closed-angle glaucoma); resistant to AChE, can cross blood-brain barrier (tertiary amine). "You cry, drool, and sweat on your 'pilow.'"	Potent stimulator of sweat, tears, and saliva Open-angle and closed-angle glaucoma, xerostomia (Sjögren syndrome)
Indirect agonists (anticholinesterases)		
Galantamine, donepezil, rivastigmine	↑ ACh.	Alzheimer disease (Alzheimer patients gallantly swim down the river)
Edrophonium	↑ ACh.	Historically used to diagnose myasthenia gravis; replaced by anti-AChR Ab (anti-acetylcholine receptor antibody) test.
Neostigmine	↑ ACh. Neo CNS = No CNS penetration (quaternary amine).	Postoperative and neurogenic ileus and urinary retention, myasthenia gravis, reversal of neuromuscular junction blockade (postoperative).
Physostigmine	↑ ACh. Physostigmine "phyxes" atropine overdose.	Antidote for anticholinergic toxicity; phreely (freely) crosses blood-brain barrier → CNS (tertiary amine).
Pyridostigmine	↑ ACh; ↑ muscle strength. Pyridostigmine gets rid of myasthenia gravis.	Myasthenia gravis (long acting); does not penetrate CNS (quaternary amine).

Note: With all cholinomimetic agents, watch for exacerbation of COPD, asthma, and peptic ulcers when giving to susceptible patients.

Cholinesterase inhibitor poisoning	Often due to organophosphates, such as parathion, that **irreversibly** inhibit AChE. Causes Diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Excitation of skeletal muscle and CNS, Lacrimation, Sweating, and Salivation. May lead to respiratory failure if untreated.	DUMBBELSS. Organophosphates are often components of insecticides; poisoning usually seen in farmers. Antidote—atropine (competitive inhibitor) + pralidoxime (regenerates AChE if given early).

Muscarinic antagonists

DRUGS	ORGAN SYSTEMS	APPLICATIONS
Atropine, homatropine, tropicamide	Eye	Produce mydriasis and cycloplegia.
Benztropine, trihexyphenidyl	CNS	**Park**inson disease ("**park** my **Benz**"). Acute dystonia.
Glycopyrrolate	GI, respiratory	Parenteral: preoperative use to reduce airway secretions. Oral: drooling, peptic ulcer.
Hyoscyamine, dicyclomine	GI	Antispasmodics for irritable bowel syndrome.
Ipratropium, tiotropium	Respiratory	COPD, asthma ("**I pra**y I can breathe soon!").
Oxybutynin, solifenacin, tolterodine	Genitourinary	Reduce bladder spasms and urge urinary incontinence (overactive bladder).
Scopolamine	CNS	Motion sickness.

Atropine

Muscarinic antagonist. Used to treat bradycardia and for ophthalmic applications.

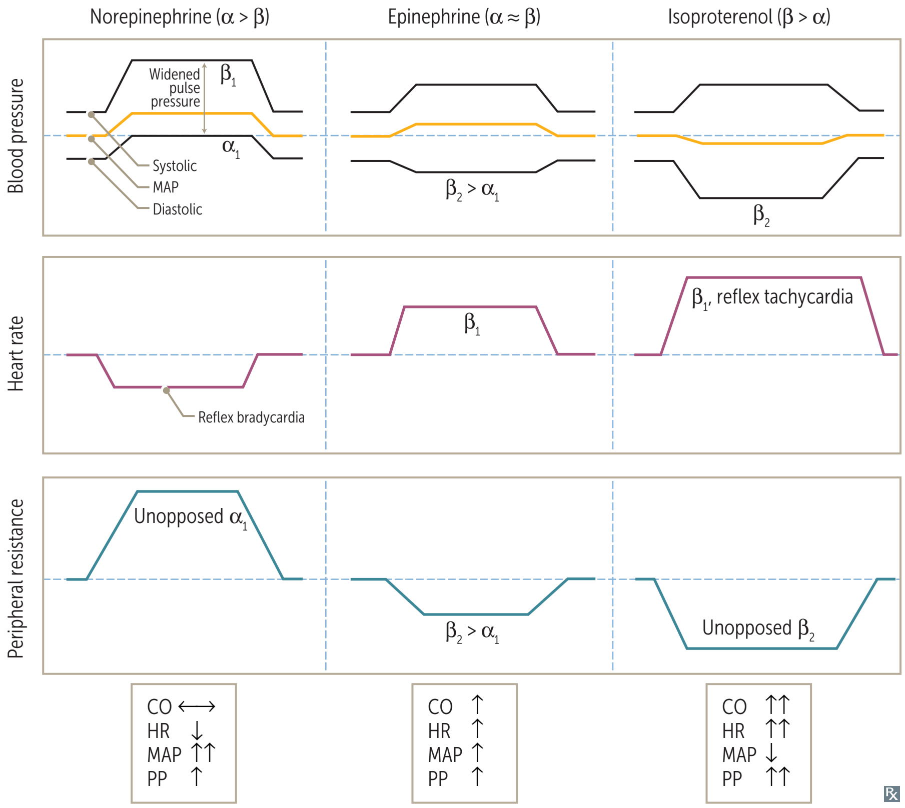
ORGAN SYSTEM	ACTION	NOTES
Eye	↑ pupil dilation, cycloplegia	Blocks **DUMBBeLSS** in cholinesterase inhibitor poisoning. Does not block excitation of skeletal muscle and CNS (mediated by nicotinic receptors).
Airway	↓ secretions	
Stomach	↓ acid secretion	
Gut	↓ motility	
Bladder	↓ urgency in cystitis	
ADVERSE EFFECTS	↑ body **temperature** (due to ↓ sweating); rapid pulse; dry mouth; **dry, flushed skin**; **cycloplegia**; constipation; **disorientation** Can cause acute angle-closure glaucoma in elderly (due to mydriasis), urinary retention in men with prostatic hyperplasia, and hyperthermia in infants.	Side effects: **Hot** as a hare **Dry** as a bone **Red** as a beet **Blind** as a bat **Mad** as a hatter Jimson weed *(Datura)* → gardener's pupil (mydriasis due to plant alkaloids)

Sympathomimetics

DRUG	ACTION	APPLICATIONS
Direct sympathomimetics		
Albuterol, salmeterol	$\beta_2 > \beta_1$	Albuterol for acute asthma or COPD. Salmeterol for long-term asthma or COPD control.
Dobutamine	$\beta_1 > \beta_2, \alpha$	Heart failure (HF) (inotropic > chronotropic), cardiac stress testing.
Dopamine	$D_1 = D_2 > \beta > \alpha$	Unstable bradycardia, HF, shock; inotropic and chronotropic effects at lower doses due to β effects; vasoconstriction at high doses due to α effects.
Epinephrine	$\beta > \alpha$	Anaphylaxis, asthma, open-angle glaucoma; α effects predominate at high doses. Significantly stronger effect at β_2-receptor than norepinephrine.
Fenoldopam	D_1	Postoperative hypertension, hypertensive crisis. Vasodilator (coronary, peripheral, renal, and splanchnic). Promotes natriuresis. Can cause hypotension and tachycardia.
Isoproterenol	$\beta_1 = \beta_2$	Electrophysiologic evaluation of tachyarrhythmias. Can worsen ischemia.
Midodrine	α_1	Autonomic insufficiency and postural hypotension. May exacerbate supine hypertension.
Mirabegron	β_3	Urinary urge incontinence or overactive bladder.
Norepinephrine	$\alpha_1 > \alpha_2 > \beta_1$	Hypotension, septic shock.
Phenylephrine	$\alpha_1 > \alpha_2$	Hypotension (vasoconstrictor), ocular procedures (mydriatic), rhinitis (decongestant).
Indirect sympathomimetics		
Amphetamine	Indirect general agonist, reuptake inhibitor, also releases stored catecholamines	Narcolepsy, obesity, ADHD.
Cocaine	Indirect general agonist, reuptake inhibitor	Causes vasoconstriction and local anesthesia. Never give β-blockers if cocaine intoxication is suspected (can lead to unopposed α_1 activation and extreme hypertension).
Ephedrine	Indirect general agonist, releases stored catecholamines	Nasal decongestion (pseudoephedrine), urinary incontinence, hypotension.

Norepinephrine vs isoproterenol

NE ↑ systolic and diastolic pressures as a result of α_1-mediated vasoconstriction → ↑ mean arterial pressure → reflex bradycardia. However, isoproterenol (rarely used) has little α effect but causes β_2-mediated vasodilation, resulting in ↓ mean arterial pressure and ↑ heart rate through β_1 and reflex activity.


Norepinephrine (α > β)
Epinephrine (α ≈ β)
Isoproterenol (β > α)
Blood pressure
Widened pulse pressure
β1
α1
Systolic
MAP
Diastolic
β2 > α1
β2
Heart rate
Reflex bradycardia
β1
β1, reflex tachycardia
Peripheral resistance
Unopposed α1
β2 > α1
Unopposed β2
CO ⟷
HR ↓
MAP ↑↑
PP ↑
CO ↑
HR ↑
MAP ↑
PP ↑
CO ↑↑
HR ↑↑
MAP ↓
PP ↑↑

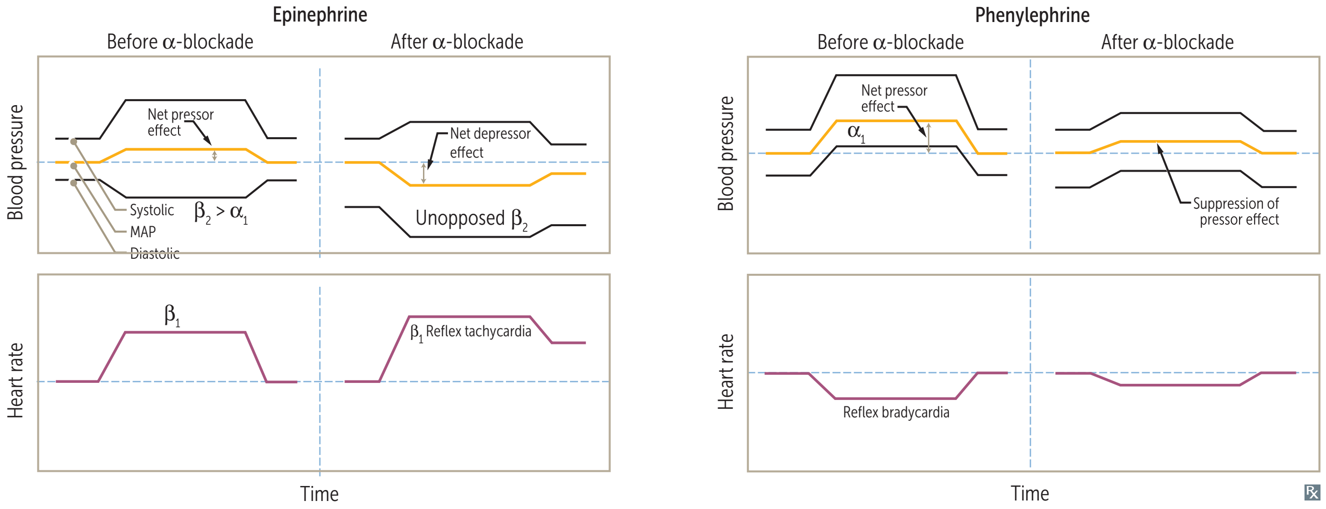
Sympatholytics (α_2-agonists)

DRUG	APPLICATIONS	ADVERSE EFFECTS
Clonidine, guanfacine	Hypertensive urgency (limited situations), ADHD, Tourette syndrome	CNS depression, bradycardia, hypotension, respiratory depression, miosis, rebound hypertension with abrupt cessation
α-methyldopa	Hypertension in pregnancy	Direct Coombs ⊕ hemolysis, SLE-like syndrome

α-blockers

DRUG	APPLICATIONS	ADVERSE EFFECTS
Nonselective		
Phenoxybenzamine	Irreversible. Pheochromocytoma (used preoperatively) to prevent catecholamine (hypertensive) crisis	Orthostatic hypotension, reflex tachycardia
Phentolamine	Reversible. Give to patients on MAO inhibitors who eat tyramine-containing foods	
α_1 selective (-osin ending)		
Prazosin, terazosin, doxazosin, tamsulosin	Urinary symptoms of BPH; PTSD (prazosin); hypertension (except tamsulosin)	1st-dose orthostatic hypotension, dizziness, headache
α_2 selective		
Mirtazapine	Depression	Sedation, ↑ serum cholesterol, ↑ appetite

Effects of α-blocker (eg, phentolamine) on BP responses to epinephrine and phenylephrine



Epinephrine response exhibits reversal of mean arterial pressure from a net increase (the α response) to a net decrease (the β_2 response).

Phenylephrine response is suppressed but not reversed because it is a “pure” α-agonist (lacks β-agonist properties).

β-blockers Acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol.

APPLICATION	ACTIONS	NOTES/EXAMPLES
Angina pectoris	↓ heart rate and contractility, resulting in ↓ O_2 consumption	
Myocardial infarction	↓ mortality	
Supraventricular tachycardia	↓ AV conduction velocity (class II antiarrhythmic)	Metoprolol, esmolol
Hypertension	↓ cardiac output, ↓ renin secretion (due to β_1-receptor blockade on JGA cells)	
Heart failure	↓ mortality (bisoprolol, carvedilol, metoprolol)	
Glaucoma	↓ production of aqueous humor	Timolol
Variceal bleeding	↓ hepatic venous pressure gradient and portal hypertension	Nadolol, propranolol
ADVERSE EFFECTS	Erectile dysfunction, cardiovascular adverse effects (bradycardia, AV block, HF), CNS adverse effects (seizures, sedation, sleep alterations), dyslipidemia (metoprolol), and asthma/COPD exacerbations	Use with caution in cocaine users due to risk of unopposed α-adrenergic receptor agonist activity
SELECTIVITY	β_1-selective antagonists ($\beta_1 > \beta_2$)—**a**cebutolol (partial agonist), **a**tenolol, **b**etaxolol, **b**isoprolol, **e**smolol, **m**etoprolol	Selective antagonists mostly go from **A** to **M** (β_1 with **1**st half of alphabet)
	Nonselective antagonists ($\beta_1 = \beta_2$)—**n**adolol, **p**indolol (partial agonist), **p**ropranolol, **t**imolol	**N**onselective antagonists mostly go from **N** to **Z** (β_2 with **2**nd half of alphabet)
	Nonselective α- and β-antagonists—carvedilol, labetalol	Nonselective α- and β-antagonists have modified suffixes (instead of "-olol")
	Nebivolol combines cardiac-selective β_1-adrenergic blockade with stimulation of β_3-receptors (activate nitric oxide synthase in the vasculature and ↓ SVR)	

Ingested seafood toxins

TOXIN	SOURCE	ACTION	SYMPTOMS	TREATMENT
Tetrodotoxin	Pufferfish.	Highly potent toxin; binds fast voltage-gated Na^+ channels in cardiac/nerve tissue, preventing depolarization.	Nausea, diarrhea, paresthesias, weakness, dizziness, loss of reflexes.	Supportive.
Ciguatoxin	Reef fish such as barracuda, snapper, and moray eel.	Opens Na^+ channels, causing depolarization.	Nausea, vomiting, diarrhea; perioral numbness; reversal of hot and cold sensations; bradycardia, heart block, hypotension.	Supportive.
Histamine (scombroid poisoning)	Spoiled dark-meat fish such as tuna, mahi-mahi, mackerel, and bonito.	Bacterial histidine decarboxylase converts histidine to histamine. Frequently misdiagnosed as fish allergy.	Mimics anaphylaxis: acute burning sensation of mouth, flushing of face, erythema, urticaria, itching. May progress to bronchospasm, angioedema, hypotension.	Antihistamines. Albuterol and epinephrine if needed.

Beers criteria

Widely used criteria developed to reduce potentially inappropriate prescribing and harmful polypharmacy in the geriatric population. Includes > 50 medications that should be avoided in elderly patients due to ↓ efficacy and/or ↑ risk of adverse events. Examples include:

- Anticholinergics, antihistamines, antidepressants, benzodiazepines, opioids (↑ risk of delirium, sedation, falls, constipation, urinary retention)
- α-blockers (↑ risk of hypotension)
- PPIs (↑ risk of C *difficile* infection)
- NSAIDs (↑ risk of GI bleeding, especially with concomitant anticoagulation)

▶ PHARMACOLOGY—TOXICITIES AND SIDE EFFECTS

Specific toxicity treatments

TOXIN	TREATMENT
Acetaminophen	N-acetylcysteine (replenishes glutathione)
AChE inhibitors, organophosphates	Atropine > pralidoxime
Antimuscarinic, anticholinergic agents	Physostigmine, control hyperthermia
Arsenic	Dimercaprol, succimer
Benzodiazepines	Flumazenil
β-blockers	Atropine, glucagon
Carbon monoxide	100% O_2, hyperbaric O_2
Copper	**Peni**cillamine, trientine (**Copper pen**ny)
Cyanide	Nitrite + thiosulfate, hydroxocobalamin
Digitalis (digoxin)	Anti-dig Fab fragments
Heparin	Protamine sulfate
Iron	De**fe**roxamine, de**fe**rasirox, de**fe**riprone
Lead	EDTA, dimercaprol, succimer, penicillamine
Mercury	Di**mer**caprol, succi**mer**
Methanol, ethylene glycol (antifreeze)	Fomepizole > ethanol, dialysis
Methemoglobin	**Meth**ylene blue, vitamin C
Opi**O**ids	Nal**O**x**O**ne
Salicylates	$NaHCO_3$ (alkalinize urine), dialysis
TCAs	$NaHCO_3$
Warfarin	Vitamin K (delayed effect), fresh frozen plasma (immediate)

Drug reactions—cardiovascular

DRUG REACTION	CAUSAL AGENTS
Coronary vasospasm	Amphetamines, cocaine, ergot alkaloids, sumatriptan
Cutaneous flushing	**V**ancomycin, **A**denosine, **N**iacin, **N**itrates, **C**a^{2+} channel blockers, **E**chinocandins (**VANNCE**)
Dilated cardiomyopathy	Anthracyclines (eg, doxorubicin, daunorubicin); prevent with dexrazoxane
Torsades de pointes	Anti**A**rrhythmics (class IA, III), anti**B**iotics (eg, macrolides), anti“**C**”ychotics (eg, haloperidol), anti**D**epressants (eg, TCAs), anti**E**metics (eg, ondansetron) (**ABCDE**)

Drug reactions—endocrine/reproductive

DRUG REACTION	CAUSAL AGENTS	NOTES
Adrenocortical insufficiency	HPA suppression 2° to glucocorticoid withdrawal	
Diabetes insipidus	Lithium, demeclocycline	
Hot flashes	Tamoxifen, clomiphene	
Hyperglycemia	**T**acrolimus, **P**rotease inhibitors, **N**iacin, **H**CTZ, **C**orticosteroids	**T**aking **P**ills **N**ecessitates **H**aving blood **C**hecked
Hypothyroidism	Lithium, amiodarone, sulfonamides	
SIADH	**C**arbamazepine, **C**yclophosphamide, **SS**RIs	**C**an't **C**oncentrate **S**erum **S**odium

Drug reactions—gastrointestinal

DRUG REACTION	CAUSAL AGENTS	NOTES
Acute cholestatic hepatitis, jaundice	Erythromycin	
Diarrhea	Acamprosate, acarbose, cholinesterase inhibitors, colchicine, erythromycin, ezetimibe, metformin, misoprostol, orlistat, pramlintide, quinidine, SSRIs	
Focal to massive hepatic necrosis	**H**alothane, ***A**manita phalloides* (death cap mushroom), **V**alproic acid, **Ac**etaminophen	Liver "**HAVAc**"
Hepatitis	Rifampin, isoniazid, pyrazinamide, statins, fibrates	
Pancreatitis	**D**idanosine, **C**orticosteroids, **A**lcohol, **V**alproic acid, **A**zathioprine, **D**iuretics (furosemide, HCTZ)	**D**rugs **C**ausing **A** **V**iolent **A**bdominal **D**istress
Pill-induced esophagitis	Bisphosphonates, ferrous sulfate, NSAIDs, potassium chloride, tetracyclines	Caustic effect minimized with upright posture and adequate water ingestion.
Pseudomembranous colitis	Ampicillin, cephalosporins, clindamycin, fluoroquinolones	Antibiotics predispose to superinfection by resistant C *difficile*

Drug reactions—hematologic

DRUG REACTION	CAUSAL AGENTS	NOTES
Agranulocytosis	Clozapine, Carbamazepine, Propylthiouracil, Methimazole, Colchicine, Ganciclovir	Can Cause Pretty Major Collapse of Granulocytes
Aplastic anemia	Carbamazepine, Methimazole, NSAIDs, Benzene, Chloramphenicol, Propylthiouracil	Can't Make New Blood Cells Properly
Direct Coombs-positive hemolytic anemia	Methyldopa, penicillin	
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Allopurinol, anticonvulsants, antibiotics, sulfa drugs	Potentially fatal delayed hypersensitivity reaction. Latency period (2–8 weeks) followed by fever, morbilliform skin rash, and frequent multiorgan involvement. Treatment: withdrawal of offending drug, corticosteroids.
Gray baby syndrome	Chloramphenicol	
Hemolysis in G6PD deficiency	Isoniazid, Sulfonamides, Dapsone, Primaquine, Aspirin, Ibuprofen, Nitrofurantoin	Hemolysis **IS D PAIN**
Megaloblastic anemia	Hydroxyurea, Phenytoin, Methotrexate, Sulfa drugs	You're having a **mega blast** with **PMS**
Thrombocytopenia	Heparin	
Thrombotic complications	Combined oral contraceptives, hormone replacement therapy, SERMs (eg, tamoxifen, raloxifene, clomiphene)	Estrogen-mediated side effect

Drug reactions—musculoskeletal/skin/connective tissue

DRUG REACTION	CAUSAL AGENTS	NOTES
Fat redistribution	Protease inhibitors, Glucocorticoids	**Fat PiG**
Gingival hyperplasia	Phenytoin, Ca^{2+} channel blockers, cyclosporine	
Hyperuricemia (gout)	Pyrazinamide, Thiazides, Furosemide, Niacin, Cyclosporine	Painful Tophi and Feet Need Care
Myopathy	Statins, fibrates, niacin, colchicine, daptomycin, hydroxychloroquine, interferon-α, penicillamine, glucocorticoids	
Osteoporosis	Corticosteroids, depot medroxyprogesterone acetate, GnRH agonists, aromatase inhibitors, anticonvulsants, heparin	
Photosensitivity	Sulfonamides, Amiodarone, Tetracyclines, 5-FU	**SAT For Photo**
Rash (Stevens-Johnson syndrome)	Anti-epileptic drugs (especially lamotrigine), allopurinol, sulfa drugs, penicillin	**Steven Johnson** has **epileptic allergy** to **sulfa drugs** and **penicillin**
SLE-like syndrome	Sulfa drugs, Hydralazine, Isoniazid, Procainamide, Phenytoin, Etanercept	Having lupus is "**SHIPP-E**"
Teeth discoloration	Tetracyclines	**Teeth**racyclines
Tendonitis, tendon rupture, and cartilage damage	Fluoroquinolones	

Drug reactions—neurologic

DRUG REACTION	CAUSAL AGENTS	NOTES
Cinchonism	Quinidine, quinine	Can present with tinnitus, hearing/vision loss, psychosis, and cognitive impairment
Parkinson-like syndrome	**A**ntipsychotics, **R**eserpine, **M**etoclopramide	Cogwheel rigidity of **ARM**
Seizures	**I**soniazid (vitamin B_6 deficiency), **B**upropion, **I**mipenem/cilastatin, **T**ramadol, **E**nflurane	With **seizures**, **I BITE** my tongue
Tardive dyskinesia	Antipsychotics, metoclopramide	

Drug reactions—renal/genitourinary

DRUG REACTION	CAUSAL AGENTS	NOTES
Fanconi syndrome	Cisplatin, ifosfamide, expired tetracyclines, tenofovir	
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide	Prevent by coadministering with mesna
Interstitial nephritis	Penicillins, furosemide, NSAIDs, proton pump inhibitors, sulfa drugs	

Drug reactions—respiratory

DRUG REACTION	CAUSAL AGENTS	NOTES
Dry cough	ACE inhibitors	
Pulmonary fibrosis	**M**ethotrexate, **N**itrofurantoin, **C**armustine, **B**leomycin, **B**usulfan, **A**miodarone	**M**y **N**ose **C**annot **B**reathe **B**ad **A**ir

Drug reactions—multiorgan

DRUG REACTION	CAUSAL AGENTS	NOTES
Antimuscarinic	Atropine, TCAs, H_1-blockers, antipsychotics	
Disulfiram-like reaction	1st-generation **S**ulfonylureas, **P**rocarbazine, certain **C**ephalosporins, **G**riseofulvin, **M**etronidazole	**S**orry **P**als, **C**an't **G**o **M**ingle.
Nephrotoxicity/ototoxicity	Aminoglycosides, vancomycin, loop diuretics, cisplatin, amphotericin B	Cisplatin toxicity may respond to amifostine.

Cytochrome P-450 interactions (selected)

Inducers (+)	Substrates	Inhibitors (–)
Chronic alcohol use	**A**nti-epileptics	**S**odium valproate
St. John's wort	**T**heophylline	**I**soniazid
Phenytoin	**W**arfarin	**C**imetidine
Phenobarbital	**O**CPs	**K**etoconazole
Nevirapine		**F**luconazole
Rifampin		**A**cute alcohol abuse
Griseofulvin		**C**hloramphenicol
Carbamazepine		**E**rythromycin (macrolides)
		Sulfonamides
		Ciprofloxacin
		Omeprazole
		Metronidazole
Chronic alcoholics **St**eal **Phen-Phen** and **Ne**ver **R**efuse **Gr**easy **Carb**s	**A**lways **T**hink **W**hen **O**utdoors	**SICKFACES**.**COM**

Sulfa drugs

Sulfonamide antibiotics, **S**ulfasalazine, **P**robenecid, **F**urosemide, **A**cetazolamide, **C**elecoxib, **T**hiazides, **S**ulfonylureas.

Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, acute interstitial nephritis, and urticaria (hives). Symptoms range from mild to life threatening.

Scary **S**ulfa **P**harm **FACTS**

▸ PHARMACOLOGY—MISCELLANEOUS

Drug names

ENDING	CATEGORY	EXAMPLE
Antimicrobial		
-azole	Ergosterol synthesis inhibitor	Ketoconazole
-bendazole	Antiparasitic/antihelminthic	Mebendazole
-cillin	Transpeptidase (penicillin-binding protein)	Ampicillin
-cycline	Protein synthesis inhibitor	Tetracycline
-ivir	Neuraminidase inhibitor	Oseltamivir
-navir	Protease inhibitor	Ritonavir
-ovir	DNA polymerase inhibitor	Acyclovir
-thromycin	Macrolide antibiotic	Azithromycin
CNS		
-ane	Inhalational general anesthetic	Halothane
-azine	Typical antipsychotic	Thioridazine
-barbital	Barbiturate	Phenobarbital
-caine	Local anesthetic	Lidocaine
-etine	SSRI	Fluoxetine
-ipramine, -triptyline	TCA	Imipramine, amitriptyline
-triptan	5-$HT_{1B/1D}$ agonist	Sumatriptan
-zepam, -zolam	Benzodiazepine	Diazepam, alprazolam
Autonomic		
-chol	Cholinergic agonist	Bethanechol, carbachol
-curium, -curonium	Nondepolarizing paralytic	Atracurium, vecuronium
-olol	β-blocker	Propranolol
-stigmine	AChE inhibitor	Neostigmine
-terol	β_2-agonist	Albuterol
-zosin	α_1-antagonist	Prazosin
Cardiovascular		
-afil	PDE-5 inhibitor	Sildenafil
-dipine	Dihydropyridine Ca^{2+} channel blocker	Amlodipine
-pril	ACE inhibitor	Captopril
-sartan	Angiotensin-II receptor blocker	Losartan
-statin	HMG-CoA reductase inhibitor	Atorvastatin
-xaban	Direct factor **Xa** inhibitor	Api**xa**ban, edo**xa**ban, rivaro**xa**ban
Other		
-dronate	Bisphosphonate	Alendronate
-glitazone	PPAR-γ activator	Rosiglitazone
-prazole	Proton pump inhibitor	Omeprazole
-prost	Prostaglandin analog	Latanoprost
-tidine	H_2-antagonist	Cimetidine
-tinib	Tyrosine kinase inhibitor	Imatinib
-tropin	Pituitary hormone	Somatotropin
-ximab	Chimeric monoclonal Ab	Basiliximab
-zumab	Humanized monoclonal Ab	Daclizumab

HIGH-YIELD PRINCIPLES IN

Public Health Sciences

- Epidemiology & Biostatistics 246
- Ethics 253
- The Well Patient 258
- Healthcare Delivery 259
- Quality and Safety 261

> *"It is a mathematical fact that fifty percent of all doctors graduate in the bottom half of their class."*
>
> —Author Unknown

> *"There are two kinds of statistics: the kind you look up and the kind you make up."*
>
> —Rex Stout

> *"On a long enough time line, the survival rate for everyone drops to zero."*
>
> —Chuck Palahniuk

> *"There are three kinds of lies: lies, damned lies, and statistics."*
>
> —Mark Twain

A heterogenous mix of epidemiology, biostatistics, ethics, law, healthcare delivery, patient safety, quality improvement, and more falls under the heading of public health sciences. Biostatistics and epidemiology are the foundations of evidence-based medicine and are very high yield. Make sure you can apply biostatistical concepts such as sensitivity, specificity, and predictive values in a problem-solving format.

Medical ethics questions may seem less concrete than questions from other disciplines. For example, if a patient does or says something, what should you do or say in response? Many medical students do not diligently study these topics because the material is felt to be easy or a matter of common sense. In our opinion, this is a missed opportunity.

In addition, the key aspects of the doctor-patient relationship (eg, communication skills) are high yield. Last, the exam has also recently added an emphasis on patient safety and quality improvement topics, which are discussed in this chapter.

▶ PUBLIC HEALTH SCIENCES—EPIDEMIOLOGY & BIOSTATISTICS

Observational studies

STUDY TYPE	DESIGN	MEASURES/EXAMPLE
Cross-sectional study	Frequency of disease and frequency of risk-related factors are assessed in the present. Asks, "What is happening?"	Disease prevalence. Can show risk factor association with disease, but does not establish causality.
Case-control study	Compares a group of people with disease to a group without disease. Looks to see if odds of prior exposure or risk factor differs by disease state. Asks, "What happened?"	Odds ratio (OR). Patients with COPD had higher odds of a history of smoking than those without COPD.
Cohort study	Compares a group with a given exposure or risk factor to a group without such exposure. Looks to see if exposure or risk factor is associated with later development of disease. Can be prospective (asks, "Who will develop disease?") or retrospective (asks, "Who developed the disease [exposed vs nonexposed]?").	Relative risk (RR). "Smokers had a higher risk of developing COPD than nonsmokers."
Twin concordance study	Compares the frequency with which both monozygotic twins vs both dizygotic twins develop the same disease.	Measures heritability and influence of environmental factors ("nature vs nurture").
Adoption study	Compares siblings raised by biological vs adoptive parents.	Measures heritability and influence of environmental factors.

Clinical trial

Experimental study involving humans. Compares therapeutic benefits of 2 or more treatments, or of treatment and placebo. Study quality improves when study is randomized, controlled, and double-blinded (ie, neither patient nor doctor knows whether the patient is in the treatment or control group). Triple-blind refers to the additional blinding of the researchers analyzing the data. Four phases ("Does the drug **SWIM**?").

DRUG TRIALS	TYPICAL STUDY SAMPLE	PURPOSE
Phase I	Small number of healthy volunteers.	"Is it **S**afe?" Assesses safety, toxicity, pharmacokinetics, and pharmacodynamics.
Phase II	Small number of patients with disease of interest.	"Does it **W**ork?" Assesses treatment efficacy, optimal dosing, and adverse effects.
Phase III	Large number of patients randomly assigned either to the treatment under investigation or to the best available treatment (or placebo).	"Is it as good or better?" Compares the new treatment to the current standard of care (any **I**mprovement?).
Phase IV	Postmarketing surveillance of patients after treatment is approved.	"Can it stay?" Detects rare or long-term adverse effects. Can result in treatment being withdrawn from **M**arket.

Evaluation of diagnostic tests

Uses 2 × 2 table comparing test results with the actual presence of disease. TP = true positive; FP = false positive; TN = true negative; FN = false negative.

Sensitivity and specificity are fixed properties of a test. PPV and NPV vary depending on disease prevalence in population being tested.

	Disease		
Test	⊕	⊖	
⊕	TP	FP	PPV = TP/(TP + FP)
⊖	FN	TN	NPV = TN/(TN + FN)
	Sensitivity = TP/(TP + FN)	Specificity = TN/(TN + FP)	Prevalence $\frac{TP + FN}{(TP + FN + FP + TN)}$

Sensitivity (true-positive rate)

Proportion of all people with disease who test positive, or the probability that when the disease is present, the test is positive.

Value approaching 100% is desirable for **ruling out** disease and indicates a **low false-negative rate**. High sensitivity test used for screening in diseases with low prevalence.

= TP / (TP + FN)

= 1 – false-negative rate

SN-N-OUT = highly **S**e**N**sitive test, when **N**egative, rules **OUT** disease

If sensitivity is 100%, then FN is zero. So, all negatives must be TNs.

Specificity (true-negative rate)

Proportion of all people without disease who test negative, or the probability that when the disease is absent, the test is negative.

Value approaching 100% is desirable for **ruling in** disease and indicates a **low false-positive rate**. High specificity test used for confirmation after a positive screening test.

= TN / (TN + FP)

= 1 – false-positive rate

SP-P-IN = highly **SP**ecific test, when **P**ositive, rules **IN** disease

If specificity is 100%, then FP is zero. So, all positives must be TPs.

Positive predictive value

Proportion of positive test results that are true positive.

Probability that a person who has a positive test result actually has the disease.

PPV = TP / (TP + FP)

PPV varies directly with pretest probability (baseline risk, such as prevalence of disease): high pretest probability → high PPV

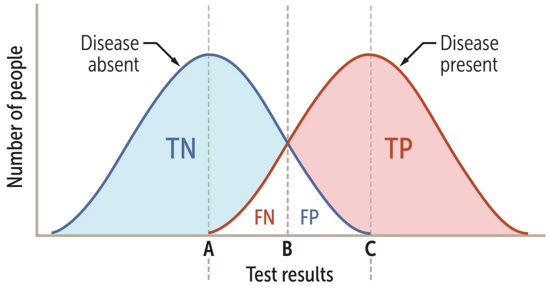
Negative predictive value

Proportion of negative test results that are true negative.

Probability that a person with a negative test result actually does not have the disease.

NPV = TN / (TN + FN)

NPV varies inversely with prevalence or pretest probability: high pretest probability → low NPV



POSSIBLE CUTOFF VALUES

A = 100% sensitivity cutoff value

B = practical compromise between specificity and sensitivity

C = 100% specificity cutoff value

Lowering the cutoff point: **B** → **A** (↑ FP ↓ FN)	↑ Sensitivity ↑ NPV ↓ Specificity ↓ PPV
Raising the cutoff point: **B** → **C** (↑ FN ↓ FP)	↑ Specificity ↑ PPV ↓ Sensitivity ↓ NPV

For example, in diabetes screening, raising the blood glucose cutoff level at which a patient is diagnosed will ↓ sensitivity, ↑ specificity, ↑ PPV, and ↓ NPV. The opposite changes occur with decreasing the blood glucose cutoff level.

Likelihood ratio

LRs can be multiplied with pretest odds of disease to estimate posttest odds. $LR^+ > 10$ and/or $LR^- < 0.1$ are easy-to-remember indicators of a very useful diagnostic test.

$$LR^+ = \frac{\text{sensitivity}}{1 - \text{specificity}} = \frac{\text{True positive rate}}{\text{False positive rate}}$$

$$LR^- = \frac{1 - \text{sensitivity}}{\text{specificity}} = \frac{\text{False negative rate}}{\text{True negative rate}}$$

Quantifying risk

Definitions and formulas are based on the classic 2 × 2 or contingency table.

		Disease	
		⊕	⊖
Risk factor or intervention	⊕	a	b
	⊖	c	d

Odds ratio

Typically used in case-control studies. OR depicts the odds of an event (eg, disease) occurring giving a certain exposure (a/b) vs the odds of an event occurring in the absence of that exposure (c/d).

$$OR = \frac{a/b}{c/d} = \frac{ad}{bc}$$

Relative risk

Typically used in cohort studies. Risk of developing disease in the exposed group divided by risk in the unexposed group (eg, if 21% of smokers develop lung cancer vs 1% of nonsmokers, RR = 21/1 = 21). For rare diseases (low prevalence), OR approximates RR.

RR = 1 → no association between exposure and disease.

RR > 1 → exposure associated with ↑ disease occurrence.

RR < 1 → exposure associated with ↓ disease occurrence.

$$RR = \frac{a/(a + b)}{c/(c + d)}$$

Attributable risk

The difference in risk between exposed and unexposed groups, or the proportion of disease occurrences that are attributable to the exposure (eg, if risk of lung cancer in smokers is 21% and risk in nonsmokers is 1%, then 20% of the lung cancer risk in smokers is attributable to smoking).

$$AR = \frac{a}{a + b} - \frac{c}{c + d}$$

Relative risk reduction

The proportion of risk reduction attributable to the intervention as compared to a control (eg, if 2% of patients who receive a flu shot develop the flu, while 8% of unvaccinated patients develop the flu, then RR = 2/8 = 0.25, and RRR = 0.75).

$$RRR = 1 - RR$$

Absolute risk reduction

The difference in risk (not the proportion) attributable to the intervention as compared to a control (eg, if 8% of people who receive a placebo vaccine develop the flu vs 2% of people who receive a flu vaccine, then ARR = 8% – 2% = 6% = .06).

$$ARR = \frac{c}{c + d} - \frac{a}{a + b}$$

Number needed to treat

Number of patients who need to be treated for 1 patient to benefit. Lower number = better treatment.

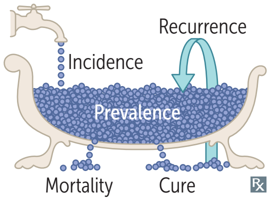
$$NNT = 1/ARR$$

Number needed to harm

Number of patients who need to be exposed to a risk factor for 1 patient to be harmed. Higher number = safer exposure.

$$NNH = 1/AR$$

Incidence vs prevalence


Recurrence
Incidence
Prevalence
Mortality
Cure

$$\text{Incidence rate} = \frac{\text{\# of new cases}}{\text{\# of people at risk}}$$ (during a specified time period)

Incidence looks at new cases (**incidents**).

$$\text{Prevalence} = \frac{\text{\# of existing cases}}{\text{Total \# of people in a population}}$$ (at a point in time)

Prev**al**ence looks at **all** current cases.

$$\frac{\text{Prevalence}}{1 - \text{prevalence}} = \text{Incidence rate} \times \text{average duration of disease}$$

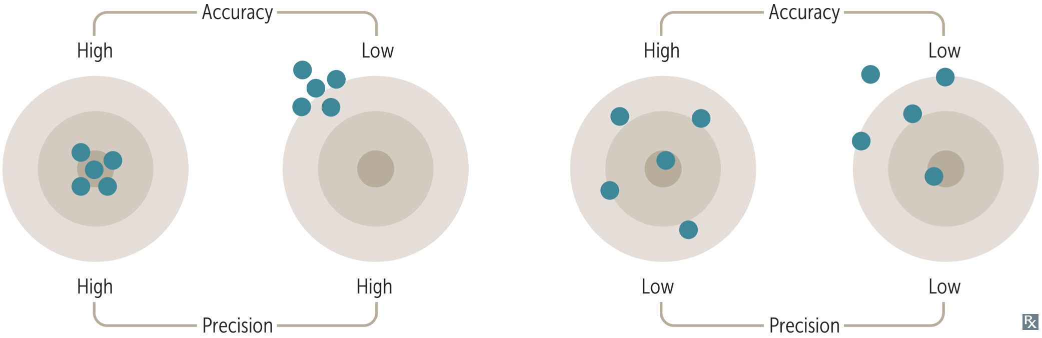
Prevalence ≈ incidence for short duration disease (eg, common cold).

Prevalence > incidence for chronic diseases, due to large # of existing cases (eg, diabetes).

Prevalence ~ pretest probability.
↑ prevalence → ↑ PPV and ↓ NPV.

Precision vs accuracy

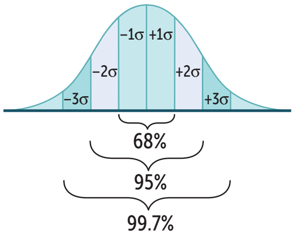
Precision (reliability)	The consistency and reproducibility of a test. The absence of random variation in a test.	Random error ↓ precision in a test. ↑ precision → ↓ standard deviation. ↑ precision → ↑ statistical power (1 – β).
Accuracy (validity)	The trueness of test measurements. The absence of systematic error or bias in a test.	Systematic error ↓ accuracy in a test.


Accuracy
High
Low
High
High
Precision
Accuracy
High
Low
Low
Low
Precision

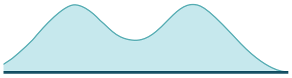
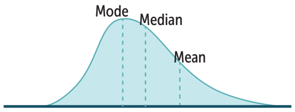
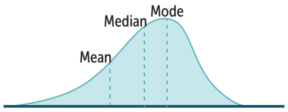
Bias and study errors

TYPE	DEFINITION	EXAMPLES	STRATEGY TO REDUCE BIAS
Recruiting participants			
Selection bias	Nonrandom sampling or treatment allocation of subjects such that study population is not representative of target population (eg, study participants included based on adherence or other criteria related to outcome). Most commonly a sampling bias.	Berkson bias—study population selected from hospital is less healthy than general population Healthy worker effect—study population is healthier than the general population Non-response bias—participating subjects differ from nonrespondents in meaningful ways	Randomization Ensure the choice of the right comparison/reference group
Performing study			
Recall bias	Awareness of disorder alters recall by subjects; common in retrospective studies.	Patients with disease recall exposure after learning of similar cases	Decrease time from exposure to follow-up
Measurement bias	Information is gathered in a systemically distorted manner.	Association between HPV and cervical cancer not observed when using non-standardized classifications Hawthorne effect—participants change their behavior in response to their awareness of being observed	Use objective, standardized, and previously tested methods of data collection that are planned ahead of time Use placebo group
Procedure bias	Subjects in different groups are not treated the same.	Patients in treatment group spend more time in highly specialized hospital units	Blinding and use of placebo reduce influence of participants and researchers on procedures and interpretation of outcomes as neither are aware of group allocation
Observer-expectancy bias	Researcher's belief in the efficacy of a treatment changes the outcome of that treatment (aka Pygmalion effect; self-fulfilling prophecy).	If observer expects treatment group to show signs of recovery, then he is more likely to document positive outcomes	
Interpreting results			
Confounding bias	When a factor is related to both the exposure and outcome, but not on the causal pathway → factor distorts or confuses effect of exposure on outcome.	Pulmonary disease is more common in coal workers than the general population; however, people who work in coal mines also smoke more frequently than the general population	Multiple/repeated studies Crossover studies (subjects act as their own controls) Matching (patients with similar characteristics in both treatment and control groups) Restriction Randomization
Lead-time bias	Early detection is confused with ↑ survival.	Early detection makes it seem as though survival has increased, but the natural history of the disease has not changed	Measure "back-end" survival (adjust survival according to the severity of disease at the time of diagnosis)

Statistical distribution

Measures of central tendency	Mean = (sum of values)/(total number of values).	Most affected by outliers (extreme values).
	Median = middle value of a list of data sorted from least to greatest.	If there is an even number of values, the median will be the average of the middle two values.
	Mode = most common value.	Least affected by outliers.
Measures of dispersion	Standard deviation = how much variability exists in a set of values, around the mean of these values. Standard error = an estimate of how much variability exists in a (theoretical) set of sample means around the true population mean.	σ = SD; n = sample size. Variance = $(SD)^2$. $SE = \sigma/\sqrt{n}$. SE ↓ as n ↑.
Normal distribution	Gaussian, also called bell-shaped. Mean = median = mode.	

Nonnormal distributions

Bimodal	Suggests two different populations (eg, metabolic polymorphism such as fast vs slow acetylators; age at onset of Hodgkin lymphoma; suicide rate by age).	
Positive skew	Typically, mean > median > mode. Asymmetry with longer tail on right.	
Negative skew	Typically, mean < median < mode. Asymmetry with longer tail on left.	

Statistical hypotheses

Null (H_0)	Hypothesis of no difference or relationship (eg, there is no association between the disease and the risk factor in the population).
Alternative (H_1)	Hypothesis of some difference or relationship (eg, there is some association between the disease and the risk factor in the population).

	Reality	
	H_1	H_0
Study rejects H_0	Power $(1 - \beta)$	α Type I error
Study does not reject H_0	β Type II error	Correct

Outcomes of statistical hypothesis testing

Correct result	Stating that there is an effect or difference when one exists (null hypothesis rejected in favor of alternative hypothesis). Stating that there is not an effect or difference when none exists (null hypothesis not rejected).	
Incorrect result		
Type I error (α)	Stating that there is an effect or difference when none exists (null hypothesis incorrectly rejected in favor of alternative hypothesis). α is the probability of making a type I error. *p* is judged against a preset α level of significance (usually 0.05). If $p < 0.05$, then there is less than a 5% chance that the data will show something that is not really there.	Also known as false-positive error. α = you accused an innocent man. You can never "prove" the alternate hypothesis, but you can reject the null hypothesis as being very unlikely.
Type II error (β)	Stating that there is not an effect or difference when one exists (null hypothesis is not rejected when it is in fact false). β is the probability of making a type II error. β is related to statistical power ($1 - \beta$), which is the probability of rejecting the null hypothesis when it is false. ↑ power and ↓ β by: ▪ ↑ sample size ▪ ↑ expected effect size ▪ ↑ precision of measurement	Also known as false-negative error. β = you blindly let the guilty man go free. If you ↑ sample size, you ↑ power. There is **power in numbers**.

Confidence interval	Range of values within which the true mean of the population is expected to fall, with a specified probability. CI for population mean = $\bar{x} \pm Z(SE)$ The 95% CI (corresponding to $\alpha = .05$) is often used. For the 95% CI, Z = 1.96. For the 99% CI, Z = 2.58.	If the 95% CI for a mean difference between 2 variables includes 0, then there is no significant difference and H_0 is not rejected. If the 95% CI for odds ratio or relative risk includes 1, H_0 is not rejected. If the CIs between 2 groups do not overlap → statistically significant difference exists. If the CIs between 2 groups overlap → usually no significant difference exists.

Common statistical tests

t-test	Checks differences between **means** of **2** groups.	**T**ea is **mean**t for **2**. Example: comparing the mean blood pressure between men and women.
ANOVA	Checks differences between means of **3** or more groups.	**3** words: **AN**alysis **O**f **VA**riance. Example: comparing the mean blood pressure between members of 3 different ethnic groups.
Chi-square (χ^2)	Checks differences between 2 or more percentages or proportions of **categorical** outcomes (not mean values).	Pronounce **Chi-tegorical**. Example: comparing the percentage of members of 3 different ethnic groups who have essential hypertension.

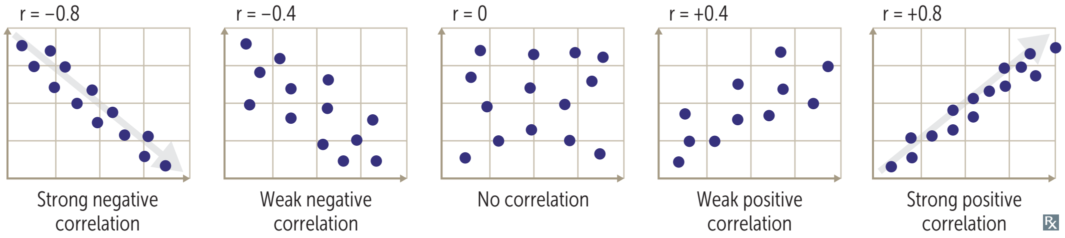
Pearson correlation coefficient

r is always between −1 and +1. The closer the absolute value of r is to 1, the stronger the linear correlation between the 2 variables.

Positive r value → positive correlation (as one variable ↑, the other variable ↑).

Negative r value → negative correlation (as one variable ↑, the other variable ↓).

Coefficient of determination = r^2 (amount of variance in one variable that can be explained by variance in another variable).



▸ BEHAVIORAL SCIENCE—ETHICS

Core ethical principles

Autonomy	Obligation to respect patients as individuals (truth-telling, confidentiality), to create conditions necessary for autonomous choice (informed consent), and to honor their preference in accepting or not accepting medical care.
Beneficence	Physicians have a special ethical (fiduciary) duty to act in the patient's best interest. May conflict with autonomy (an informed patient has the right to decide) or what is best for society (eg, mandatory TB treatment). Traditionally, patient interest supersedes.
Nonmaleficence	"Do no harm." Must be balanced against beneficence; if the benefits outweigh the risks, a patient may make an informed decision to proceed (most surgeries and medications fall into this category).
Justice	To treat persons fairly and equitably. This does not always imply equally (eg, triage).

Informed consent

A process (not just a document/signature) that requires:
- Disclosure: discussion of pertinent information
- Understanding: ability to comprehend
- Capacity: ability to reason and make one's own decisions (distinct from competence, a legal determination)
- Voluntariness: freedom from coercion and manipulation

Patients must have an intelligent understanding of their diagnosis and the risks/benefits of proposed treatment and alternative options, including no treatment.

Patient must be informed that he or she can revoke written consent at any time, even orally.

Exceptions to informed consent:
- Patient lacks decision-making capacity or is legally incompetent
- Implied consent in an emergency
- Therapeutic privilege—withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity
- Waiver—patient explicitly waives the right of informed consent

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Consent for minors

A minor is generally any person < 18 years old. Parental consent laws in relation to healthcare vary by state. In general, parental consent should be obtained, but exceptions exist for emergency treatment (eg, blood transfusions) or if minor is legally emancipated (eg, married, self supporting, or in the military).

Situations in which parental consent is usually not required:
- **Sex** (contraception, STIs, pregnancy)
- **Drugs** (substance abuse)
- **Rock and roll** (emergency/trauma)

Physicians should always encourage healthy minor-guardian communication.

Physician should seek a minor's assent even if their consent is not required.

Decision-making capacity

Physician must determine whether the patient is psychologically and legally capable of making a particular healthcare decision. Note that decisions made with capacity cannot be revoked simply if the patient later loses capacity.

Capacity is determined by a physician for a specific healthcare-related decision (eg, to refuse medical care). Competency is determined by a judge and usually refers to more global categories of decision making (eg, legally unable to make any healthcare-related decision).

Components:
- Patient is ≥ 18 years old or otherwise legally emancipated
- Patient makes and communicates a choice
- Patient is informed (knows and understands)
- Decision remains stable over time
- Decision is consistent with patient's values and goals, not clouded by a mood disorder
- Decision is not a result of altered mental status (eg, delirium, psychosis, intoxication)

Advance directives	Instructions given by a patient in anticipation of the need for a medical decision. Details vary per state law.
Oral advance directive	Incapacitated patient's prior oral statements commonly used as guide. Problems arise from variance in interpretation. If patient was informed, directive was specific, patient made a choice, and decision was repeated over time to multiple people, then the oral directive is more valid.
Written advance directive	Specifies specific healthcare interventions that a patient anticipates he or she would accept or reject during treatment for a critical or life-threatening illness. A living will is an example.
Medical power of attorney	Patient designates an agent to make medical decisions in the event that he/she loses decision-making capacity. Patient may also specify decisions in clinical situations. Can be revoked by patient if decision-making capacity is intact. More flexible than a living will.
Do not resuscitate order	DNR order applies to cardiopulmonary resuscitation (CPR). Other resuscitative measures that follow (cardioversion, intubation) are also typically avoided.
Surrogate decision-maker	If a patient loses decision-making capacity and has not prepared an advance directive, individuals (surrogates) who know the patient must determine what the patient would have done. Priority of surrogates: **spouse** → adult **Ch**ildren → **P**arents → **S**iblings → other relatives (the **spouse ChiPS** in).
Confidentiality	Confidentiality respects patient privacy and autonomy. If patient is not present or is incapacitated, disclosing information to family and friends should be guided by professional judgment of patient's best interest. The patient may voluntarily waive the right to confidentiality (eg, insurance company request). General principles for exceptions to confidentiality: ▪ Potential physical harm to others is serious and imminent ▪ Likelihood of harm to self is great ▪ No alternative means exist to warn or to protect those at risk ▪ Physicians can take steps to prevent harm Examples of exceptions to patient confidentiality (many are state-specific) include the following ("The physician's good judgment **SAVED** the day"): ▪ **S**uicidal/homicidal patients ▪ **A**buse (children, elderly, and/or prisoners) ▪ Duty to protect—State-specific laws that sometimes allow physician to inform or somehow protect potential **V**ictim from harm. ▪ **E**pileptic patients and other impaired automobile drivers. ▪ Reportable **D**iseases (eg, STIs, hepatitis, food poisoning); physicians may have a duty to warn public officials, who will then notify people at risk. Dangerous communicable diseases, such as TB or Ebola, may require involuntary treatment.

Ethical situations

SITUATION	APPROPRIATE RESPONSE
Patient is not adherent.	Attempt to identify the reason for nonadherence and determine his/her willingness to change; do not coerce the patient into adhering and do not refer him/her to another physician.
Patient desires an unnecessary procedure.	Attempt to understand why the patient wants the procedure and address underlying concerns. Do not refuse to see the patient and do not refer him/her to another physician. Avoid performing unnecessary procedures.
Patient has difficulty taking medications.	Provide written instructions; attempt to simplify treatment regimens; use teach-back method (ask patient to repeat regimen back to physician) to ensure comprehension.
Family members ask for information about patient's prognosis.	Avoid discussing issues with relatives without the patient's permission.
A patient's family member asks you not to disclose the results of a test if the prognosis is poor because the patient will be "unable to handle it."	Attempt to identify why the family member believes such information would be detrimental to the patient's condition. Explain that as long as the patient has decision-making capacity and does not indicate otherwise, communication of information concerning his/her care will not be withheld. However, if you believe the patient might seriously harm himself or others if informed, then you may invoke therapeutic privilege and withhold the information.
A 17-year-old girl is pregnant and requests an abortion.	Many states require parental notification or consent for minors for an abortion. Unless there are specific medical risks associated with pregnancy, a physician should not sway the patient's decision for an elective abortion (regardless of maternal age or fetal condition).
A 15-year-old girl is pregnant and wants to keep the child. Her parents want you to tell her to give the child up for adoption.	The patient retains the right to make decisions regarding her child, even if her parents disagree. Provide information to the teenager about the practical issues of caring for a baby. Discuss the options, if requested. Encourage discussion between the teenager and her parents to reach the best decision.
A terminally ill patient requests physician assistance in ending his/her own life.	In the overwhelming majority of states, refuse involvement in any form of physician-assisted suicide. Physicians may, however, prescribe medically appropriate analgesics that coincidentally shorten the patient's life.
Patient is suicidal.	Assess the seriousness of the threat. If it is serious, suggest that the patient remain in the hospital voluntarily; patient can be hospitalized involuntarily if he/she refuses.
Patient states that he/she finds you attractive.	Ask direct, closed-ended questions and use a chaperone if necessary. Romantic relationships with patients are never appropriate.
A woman who had a mastectomy says she now feels "ugly."	Find out why the patient feels this way. Do not offer falsely reassuring statements (eg, "You still look good").
Patient is angry about the long time he/she spent in the waiting room.	Acknowledge the patient's anger, but do not take a patient's anger personally. Apologize for any inconvenience. Stay away from efforts to explain the delay.
Patient is upset with the way he/she was treated by another doctor.	Suggest that the patient speak directly to that physician regarding his/her concerns. If the problem is with a member of the office staff, tell the patient you will speak to that person.
An invasive test is performed on the wrong patient.	Regardless of the outcome, a physician is ethically obligated to inform a patient that a mistake has been made.

Ethical situations *(continued)*

SITUATION	APPROPRIATE RESPONSE
A patient requires a treatment not covered by his/her insurance.	Never limit or deny care because of the expense in time or money. Discuss all treatment options with patients, even if some are not covered by their insurance companies.
A 7-year-old boy loses a sister to cancer and now feels responsible.	At ages 5–7, children begin to understand that death is permanent, that all life functions end completely at death, and that everything that is alive eventually dies. Provide a direct, concrete description of his sister's death. Avoid clichés and euphemisms. Reassure that the boy is not responsible. Identify and normalize fears and feelings. Encourage play and healthy coping behaviors (eg, remembering her in his own way).
Patient is victim of intimate partner violence.	Ask if patient is safe and has an emergency plan. Do not necessarily pressure patient to leave his or her partner, or disclose the incident to the authorities (unless required by state law).
Patient wants to try alternative or holistic medicine.	Find out why and allow patient to do so as long as there are no contraindications, medication interactions, or adverse effects to the new treatment.
Physician colleague presents to work impaired.	If impaired or incompetent, colleague is a threat to patient safety. Report the situation to local supervisory personnel. Should the organization fail to take action, alert the state licensing board.
Patient is officially determined to suffer brain death. Patient's family insists on maintaining life support indefinitely because patient is still moving when touched.	Gently explain to family that there is no chance of recovery, and that brain death is equivalent to death. Movement is due to spinal arc reflex and is not voluntary. Bring case to appropriate ethics board regarding futility of care and withdrawal of life support.
A pharmaceutical company offers you a sponsorship in exchange for advertising its new drug.	Reject this offer. Generally, decline gifts and sponsorships to avoid any appearance of conflict of interest. The AMA Code of Ethics does make exceptions for gifts directly benefitting patients; gifts of minimal value; special funding for medical education of students, residents, fellows; grants whose recipients are chosen by independent institutional criteria; and funds that are distributed without attribution to sponsors.
An adult refuses care because it is against his/her religious beliefs.	Work with the patient by either explaining the treatment or pursuing alternative treatments. However, a physician should never force a competent adult to receive care if it is contrary to the patient's religious beliefs.
Mother and 15-year-old daughter are unresponsive following a car accident and are bleeding internally. Father says do not transfuse because they are Jehovah's Witnesses.	Transfuse daughter, but do not transfuse mother. Emergent care can be refused by the healthcare proxy for an adult, particularly when patient preferences are known or reasonably inferred, but not for a minor.

▸ PUBLIC HEALTH SCIENCES—THE WELL PATIENT

Early developmental milestones

Milestone dates are ranges that have been approximated and vary by source. Children not meeting milestones may need assessment for potential developmental delay.

AGE	MOTOR	SOCIAL	VERBAL/COGNITIVE
Infant	**Parents**	**Start**	**Observing,**
0–12 mo	Primitive reflexes disappear—Moro (by 3 mo), rooting (by 4 mo), palmar (by 6 mo), Babinski (by 12 mo) Posture—lifts head up prone (by 1 mo), rolls and sits (by 6 mo), crawls (by 8 mo), stands (by 10 mo), walks (by 12–18 mo) Picks—passes toys hand to hand (by 6 mo), Pincer grasp (by 10 mo) Points to objects (by 12 mo)	Social smile (by 2 mo) Stranger anxiety (by 6 mo) Separation anxiety (by 9 mo)	Orients—first to voice (by 4 mo), then to name and gestures (by 9 mo) Object permanence (by 9 mo) Oratory—says "mama" and "dada" (by 10 mo)
Toddler	**Child**	**Rearing**	**Working,**
12–36 mo	Cruises, takes first steps (by 12 mo) Climbs stairs (by 18 mo) Cubes stacked—number = age (yr) × 3 Cutlery—feeds self with fork and spoon (by 20 mo) Kicks ball (by 24 mo)	Recreation—parallel play (by 24–36 mo) Rapprochement—moves away from and returns to mother (by 24 mo) Realization—core gender identity formed (by 36 mo)	Words—200 words by age 2 (2 zeros), 2-word sentences
Preschool	**Don't**	**Forget, they're still**	**Learning!**
3–5 yr	Drive—tricycle (3 wheels at 3 yr) Drawings—copies line or circle, stick figure (by 4 yr) Dexterity—hops on one foot (by 4 yr), uses buttons or zippers, grooms self (by 5 yr)	Freedom—comfortably spends part of day away from mother (by 3 yr) Friends—cooperative play, has imaginary friends (by 4 yr)	Language—1000 words by age 3 (3 zeros), uses complete sentences and prepositions (by 4 yr) Legends—can tell detailed stories (by 4 yr)

Car seats for children

Children should ride in rear-facing car seats until they are 2 years old and in car seats with a harness until they are 4 years. Older children should use a booster seat until they are 8 years old or until the seat belt fits properly. Children < 12 years old should not ride in a seat with a front-facing airbag.

Changes in the elderly

Sexual changes:
- Men—slower erection/ejaculation, longer refractory period.
- Women—vaginal shortening, thinning, and dryness.

Sleep patterns: ↓ REM and slow-wave sleep; ↑ sleep onset latency; ↑ early awakenings.
↑ suicide rate.
↓ vision and hearing.
↓ immune response.
↓ renal, pulmonary, and GI function.
↓ muscle mass, ↑ fat.
Intelligence does not decrease.

▶ PUBLIC HEALTH SCIENCES—HEALTHCARE DELIVERY

Disease prevention

Primary	Prevent disease before it occurs (eg, HPV vaccination)	
Secondary	Screen early for and manage existing but asymptomatic disease (eg, Pap smear for cervical cancer)	
Tertiary	Treatment to reduce complications from disease that is ongoing or has long-term effects (eg, chemotherapy)	**Quaternary**—identifying patients at risk of unnecessary treatment, protecting from the harm of new interventions (eg, electronic sharing of patient records to avoid duplicating recent laboratory and imaging studies)

Major medical insurance plans

Health Maintenance Organization	Patients are restricted (except in emergencies) to a limited panel of providers who are in the network. Payment is denied for any service that does not meet established, evidence-based guidelines. Requires referral from primary care provider to see a specialist.
Point of Service	Patients are allowed to see providers outside of the network, but have higher out-of-pocket costs, including higher copays and deductibles, for out-of-network services. Requires referral from primary care provider to see a specialist.
Preferred Provider Organization	Patients are allowed to see physicians who are within or outside of the network. All services have higher copays and deductibles. Does not require referral from primary care provider to see a specialist.
Exclusive Provider Organization	Patients are limited (except in emergencies) to a network of doctors, specialists, and hospitals. Does not require referral from primary care provider to see a specialist.

Healthcare payment models

Capitation	Physicians receive a set amount per patient assigned to them per period of time, regardless of how much the patient uses the healthcare system.
Discounted fee-for-service	Patient pays for each individual service at a predetermined, discounted rate.
Global payment	Patient pays for all expenses associated with a single incident of care with a single payment. Most commonly used during elective surgeries, as it covers the cost of surgery as well as the necessary pre- and postoperative visits.

Medicare and Medicaid

Medicare and Medicaid—federal social healthcare programs that originated from amendments to the Social Security Act.

Medicare is available to patients ≥ 65 years old, < 65 with certain disabilities, and those with end-stage renal disease.

Medicaid is joint federal and state health assistance for people with limited income and/or resources.

Medicar**E** is for **E**lderly.
Medicai**D** is for **D**estitute.

The 4 parts of Medicare:

- Part **A**: Hospit**A**l insurance, home hospice care
- Part **B**: **B**asic medical **b**ills (eg, doctor's fees, diagnostic testing)
- Part **C**: (parts A + B = **C**ombo) delivered by approved private **c**ompanies
- Part **D**: Prescription **D**rugs

Hospice care

Medical care focused on providing comfort and palliation instead of definitive cure. Available to patients on Medicare or Medicaid and in most private insurance plans whose life expectancy is < 6 months.

During end-of-life care, priority is given to improving the patient's comfort and relieving pain, and care often includes opioid medications. Facilitating comfort is prioritized over potential side effects (eg, respiratory depression). This prioritization of positive effects over negative effects is known as the principle of double effect.

Common causes of death (US) by age

	< 1 YR	1–14 YR	15–34 YR	35–44 YR	45–64 YR	65+ YR
#1	Congenital malformations	Unintentional injury	Unintentional injury	Unintentional injury	Cancer	Heart disease
#2	Preterm birth	Cancer	Suicide	Cancer	Heart disease	Cancer
#3	Maternal pregnancy complication	Congenital malformations	Homicide	Heart disease	Unintentional injury	Chronic respiratory disease

Hospitalized conditions with frequent readmissions

	MEDICARE	MEDICAID	PRIVATE INSURANCE	UNINSURED
#1	Congestive HF	Mood disorders	Maintenance of chemotherapy or radiotherapy	Mood disorders
#2	Septicemia	Schizophrenia/ psychotic disorders	Mood disorders	Alcohol-related disorders
#3	Pneumonia	Diabetes mellitus with complications	Complications of surgical procedures or medical care	Diabetes mellitus with complications

Readmission for any reason within 30 days of original admission.

▸ PUBLIC HEALTH SCIENCES—QUALITY AND SAFETY

Safety culture

Organizational environment in which everyone can freely bring up safety concerns without fear of censure. Facilitates error identification.

Event reporting systems collect data on errors for internal and external monitoring.

Human factors design

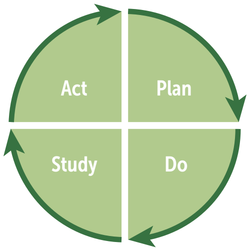
Forcing functions (those that prevent undesirable actions [eg, connecting feeding syringe to IV tubing]) are the most effective.
Standardization improves process reliability (eg, clinical pathways, guidelines, checklists).
Simplification reduces wasteful activities (eg, consolidating electronic medical records [EMRs]).

Deficient designs hinder workflow and lead to staff workarounds that bypass safety features (eg, patient ID barcodes affixed to computers due to unreadable wristbands).

PDSA cycle

Process improvement model to test changes in real clinical setting. Impact on patients:

- **P**lan—define problem and solution
- **D**o—test new process
- **S**tudy—measure and analyze data
- **A**ct—integrate new process into regular workflow

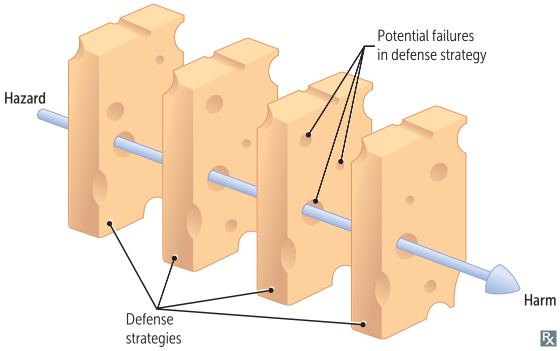


Quality measurements Plotted on run and control charts.

	MEASURE	EXAMPLE
Outcome	Impact on patients	Average HbA_{1c} of patients with diabetes
Process	Performance of system as planned	Percentage of target patients whose HbA_{1c} was measured in the past 6 months
Balancing	Impact on other systems/outcomes	Incidence of hypoglycemia among those patients

Swiss cheese model

Focuses on systems and conditions rather than an individual's error. The risk of a threat becoming a reality is mitigated by differing layers and types of defenses. Patient harm can occur despite multiple safeguards when "the holes in the cheese line up."


Potential failures in defense strategy
Hazard
Harm
Defense strategies

Types of medical errors	May involve patient identification, diagnosis, monitoring, nosocomial infection, medications, procedures, devices, documentation, handoffs. Errors causing harmful outcomes must be disclosed to patients.	
Active error	Occurs at level of frontline operator (eg, wrong IV pump dose programmed).	Immediate impact.
Latent error	Occurs in processes indirect from operator but impacts patient care (eg, different types of IV pumps used within same hospital).	Accident waiting to happen.

Medical error analysis

Root cause analysis	Uses records and participant interviews to identify all the underlying problems that led to an error. Categories of causes include process, people (providers or patients), environment, equipment, materials, management.	**R**etrospective approach applied after failure event to prevent recurrence. Plotted on fishbone (Ishikawa, cause-and-effect) diagram. Fix causes with corrective action plan.
Failure mode and effects analysis	Uses inductive reasoning to identify all the ways a process might fail and prioritize these by their probability of occurrence and impact on patients.	**F**orward-looking approach applied before process implementation to prevent failure occurrence.

SECTION III

High-Yield Organ Systems

"Symptoms, then, are in reality nothing but the cry from suffering organs."
—Jean-Martin Charcot

"Man is an intelligence in servitude to his organs."
—Aldous Huxley

"Learn that you are a machine, your heart an engine, your lungs a fanning machine and a sieve, your brain with its two lobes an electric battery."
—Andrew T. Still

- Approaching the Organ Systems 264
- Cardiovascular 267
- Endocrine 311
- Gastrointestinal 343
- Hematology and Oncology 385
- Musculoskeletal, Skin, and Connective Tissue 423
- Neurology and Special Senses 459
- Psychiatry 523
- Renal 547
- Reproductive 579
- Respiratory 625

▸ APPROACHING THE ORGAN SYSTEMS

In this section, we have divided the High-Yield Facts into the major **Organ Systems.** Within each Organ System are several subsections, including **Embryology, Anatomy, Physiology, Pathology,** and **Pharmacology.** As you progress through each Organ System, refer back to information in the previous subsections to organize these basic science subsections into a "vertically integrated" framework for learning. Below is some general advice for studying the organ systems by these subsections.

Embryology

Relevant embryology is included in each organ system subsection. Embryology tends to correspond well with the relevant anatomy, especially with regard to congenital malformations.

Anatomy

Several topics fall under this heading, including gross anatomy, histology, and neuroanatomy. Do not memorize all the small details; however, do not ignore anatomy altogether. Review what you have already learned and what you wish you had learned. Many questions require two or more steps. The first step is to identify a structure on anatomic cross section, electron micrograph, or photomicrograph. The second step may require an understanding of the clinical significance of the structure.

When studying, stress clinically important material. For example, be familiar with gross anatomy and radiologic anatomy related to specific diseases (eg, Pancoast tumor, Horner syndrome), traumatic injuries (eg, fractures, sensory and motor nerve deficits), procedures (eg, lumbar puncture), and common surgeries (eg, cholecystectomy). There are also many questions on the exam involving x-rays, CT scans, and neuro MRI scans. Many students suggest browsing through a general radiology atlas, pathology atlas, and histology atlas. Focus on learning basic anatomy at key levels in the body (eg, sagittal brain MRI; axial CT of the midthorax, abdomen, and pelvis). Basic neuroanatomy (especially pathways, blood supply, and functional anatomy), associated neuropathology, and neurophysiology have good yield. Please note that many of the photographic images in this book are for illustrative purposes and are not necessarily reflective of Step 1 emphasis.

Physiology

The portion of the examination dealing with physiology is broad and concept oriented and thus does not lend itself as well to fact-based review. Diagrams are often the best study aids, especially given the increasing number of questions requiring the interpretation of diagrams. Learn to apply basic physiologic relationships in a variety of ways (eg, the Fick equation, clearance equations). You are seldom asked to perform complex calculations. Hormones are the focus of many questions, so learn their sites of production and action as well as their regulatory mechanisms.

A large portion of the physiology tested on the USMLE Step 1 is clinically relevant and involves understanding physiologic changes associated with pathologic processes (eg, changes in pulmonary function with COPD). Thus, it is worthwhile to review the physiologic changes that are found with common pathologies of the major organ systems (eg, heart, lungs, kidneys, GI tract) and endocrine glands.

Pathology

Questions dealing with this discipline are difficult to prepare for because of the sheer volume of material involved. Review the basic principles and hallmark characteristics of the key diseases. Given the clinical orientation of Step 1, it is no longer sufficient to know only the "buzzword" associations of certain diseases (eg, café-au-lait macules and neurofibromatosis); you must also know the clinical descriptions of these findings.

Given the clinical slant of the USMLE Step 1, it is also important to review the classic presenting signs and symptoms of diseases as well as their associated laboratory findings. Delve into the signs, symptoms, and pathophysiology of major diseases that have a high prevalence in the United States (eg, alcoholism, diabetes, hypertension, heart failure, ischemic heart disease, infectious disease). Be prepared to think one step beyond the simple diagnosis to treatment or complications.

The examination includes a number of color photomicrographs and photographs of gross specimens that are presented in the setting of a brief clinical history. However, read the question and the choices carefully before looking at the illustration, because the history will help you identify the pathologic process. Flip through an illustrated pathology textbook, color atlases, and appropriate Web sites in order to look at the pictures in the days before the exam. Pay attention to potential clues such as age, sex, ethnicity, occupation, recent activities and exposures, and specialized lab tests.

Pharmacology

Preparation for questions on pharmacology is straightforward. Memorizing all the key drugs and their characteristics (eg, mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the "classic" and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

▶ NOTES

HIGH-YIELD SYSTEMS

Cardiovascular

"As for me, except for an occasional heart attack, I feel as young as I ever did."

—Robert Benchley

"Hearts will never be practical until they are made unbreakable."

—The Wizard of Oz

"As the arteries grow hard, the heart grows soft."

—H. L. Mencken

"Nobody has ever measured, not even poets, how much the heart can hold."

—Zelda Fitzgerald

"Only from the heart can you touch the sky."

—Rumi

"It is not the size of the man but the size of his heart that matters."

—Evander Holyfield

▸ Embryology 268
▸ Anatomy 271
▸ Physiology 272
▸ Pathology 288
▸ Pharmacology 304

▶ CARDIOVASCULAR—EMBRYOLOGY

Heart embryology

EMBRYONIC STRUCTURE	GIVES RISE TO
Truncus arteriosus	Ascending aorta and pulmonary trunk
Bulbus cordis	Smooth parts (outflow tract) of left and right ventricles
Endocardial cushion	Atrial septum, membranous interventricular septum; AV and semilunar valves
Primitive atrium	Trabeculated part of left and right atria
Primitive ventricle	Trabeculated part of left and right ventricles
Primitive pulmonary vein	Smooth part of left atrium
Left horn of sinus venosus	Coronary sinus
Right horn of sinus venosus	Smooth part of right atrium (sinus venarum)
Right common cardinal vein and right anterior cardinal vein	Superior vena cava (SVC)

Heart morphogenesis

First functional organ in vertebrate embryos; beats spontaneously by week 4 of development.

Cardiac looping

Primary heart tube loops to establish left-right polarity; begins in week 4 of gestation.

Defect in left-right dynein (involved in L/R asymmetry) can lead to dextrocardia, as seen in Kartagener syndrome (primary ciliary dyskinesia).

Septation of the chambers

Atria

❶ Septum primum grows toward endocardial cushions, narrowing foramen primum.

❷ Foramen secundum forms in septum primum (foramen primum disappears).

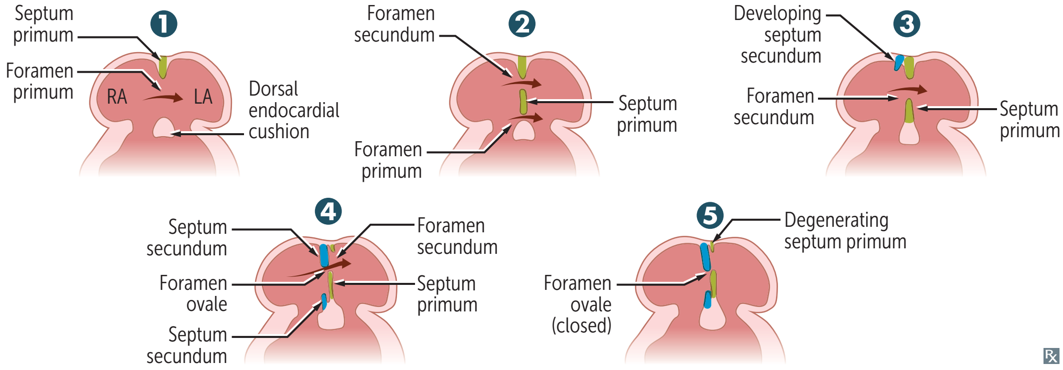
❸ Septum secundum develops as foramen secundum maintains right-to-left shunt.

❹ Septum secundum expands and covers most of the foramen secundum. The residual foramen is the foramen ovale.

❺ Remaining portion of septum primum forms valve of foramen ovale.

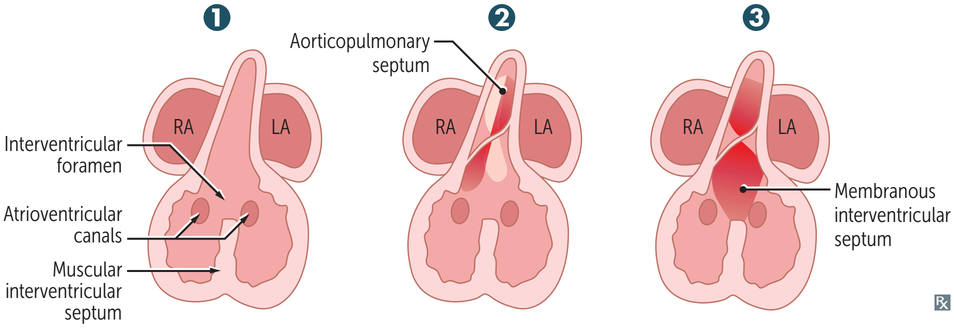
6. (Not shown) Septum secundum and septum primum fuse to form the atrial septum.
7. (Not shown) Foramen ovale usually closes soon after birth because of ↑ LA pressure.

Patent foramen ovale—caused by failure of septum primum and septum secundum to fuse after birth; most are left untreated. Can lead to paradoxical emboli (venous thromboemboli that enter systemic arterial circulation), similar to those resulting from an ASD.


❶
Septum primum
Foramen primum
RA
LA
Dorsal endocardial cushion
❷
Foramen secundum
Septum primum
Foramen primum
❸
Developing septum secundum
Foramen secundum
Septum primum
❹
Septum secundum
Foramen ovale
Septum secundum
Foramen secundum
Septum primum
❺
Degenerating septum primum
Foramen ovale (closed)

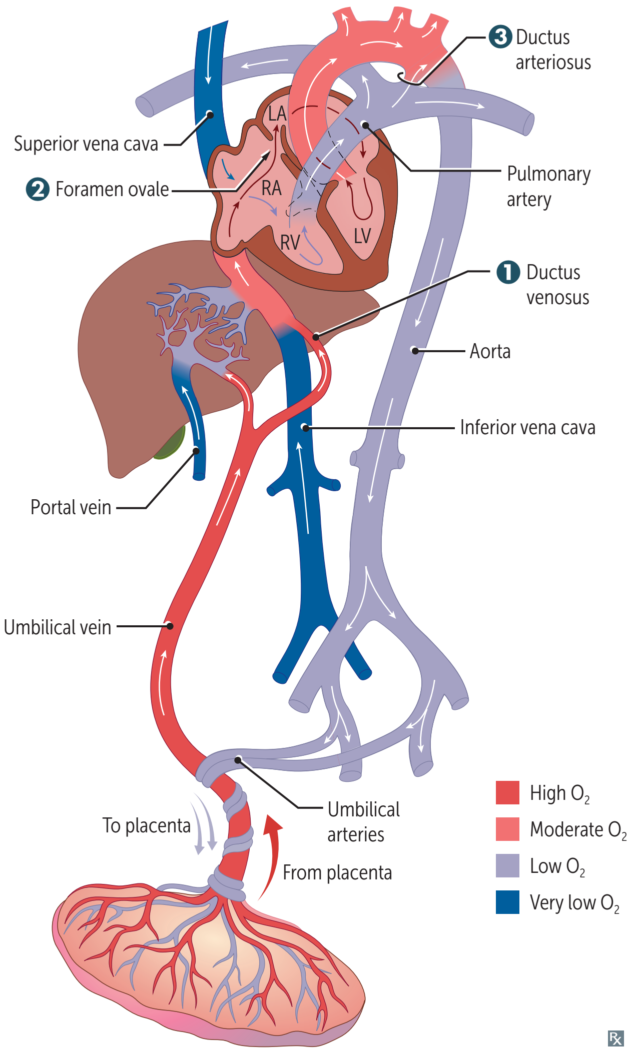
Heart morphogenesis *(continued)*

Ventricles	❶ Muscular interventricular septum forms. Opening is called interventricular foramen. ❷ Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum, closing interventricular foramen. ❸ Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum.	**Ventricular septal defect**—most common congenital cardiac anomaly, usually occurs in membranous septum.


❶
❷
❸
Aorticopulmonary septum
RA
LA
RA
LA
RA
LA
Interventricular foramen
Atrioventricular canals
Muscular interventricular septum
Membranous interventricular septum

Outflow tract formation	Neural crest and endocardial cell migrations → truncal and bulbar ridges that spiral and fuse to form aorticopulmonary septum → ascending aorta and pulmonary trunk.	Conotruncal abnormalities associated with failure of neural crest cells to migrate: ▪ Transposition of great vessels. ▪ Tetralogy of Fallot. ▪ Persistent truncus arteriosus.
Valve development	Aortic/pulmonary: derived from endocardial cushions of outflow tract. Mitral/tricuspid: derived from fused endocardial cushions of the AV canal.	Valvular anomalies may be stenotic, regurgitant, atretic (eg, tricuspid atresia), or displaced (eg, Ebstein anomaly).

Fetal circulation


❸ Ductus arteriosus
Superior vena cava
LA
❷ Foramen ovale
RA
Pulmonary artery
RV
LV
❶ Ductus venosus
Aorta
Inferior vena cava
Portal vein
Umbilical vein
Umbilical arteries
To placenta
From placenta
High O_2
Moderate O_2
Low O_2
Very low O_2

Blood in umbilical vein has a Po_2 of ≈ 30 mm Hg and is ≈ 80% saturated with O_2. Umbilical arteries have low O_2 saturation.

3 important shunts:

❶ Blood entering fetus through the umbilical vein is conducted via the **ductus venosus** into the IVC, bypassing hepatic circulation.

❷ Most of the highly Oxygenated blood reaching the heart via the IVC is directed through the **foramen Ovale** and pumped into the aorta to supply the head and body.

❸ Deoxygenated blood from the SVC passes through the RA → RV → main pulmonary artery → **Ductus arteriosus** → Descending aorta; shunt is due to high fetal pulmonary artery resistance (due partly to low O_2 tension).

At birth, infant takes a breath; ↓ resistance in pulmonary vasculature → ↑ left atrial pressure vs right atrial pressure; foramen ovale closes (now called fossa ovalis); ↑ in O_2 (from respiration) and ↓ in prostaglandins (from placental separation) → closure of ductus arteriosus.

Indomethacin helps close PDA → ligamentum arteriosum (remnant of ductus arteriosus).

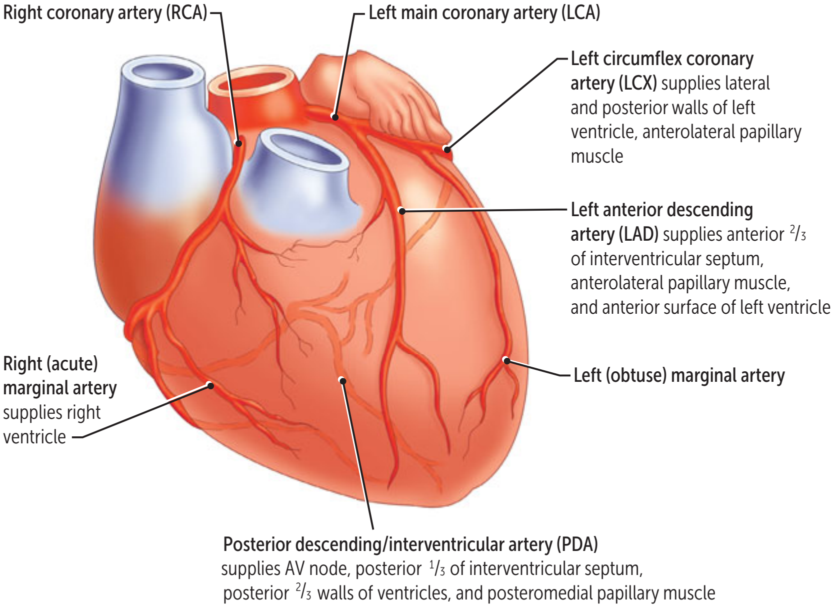
Prostaglandins E_1 and E_2 kEEp PDA open.

Fetal-postnatal derivatives

AllaNtois → urachus	MediaN umbilical ligament	Urachus is part of allantoic duct between bladder and umbilicus.
Ductus arteriosus	Ligamentum arteriosum	
Ductus venosus	Ligamentum venosum	
Foramen ovale	Fossa ovalis	
Notochord	Nucleus pulposus	
UmbiLical arteries	MediaL umbilical ligaments	
Umbilical vein	Ligamentum teres hepatis (round ligament)	Contained in falciform ligament.

▸ CARDIOVASCULAR—ANATOMY

Anatomy of the heart


Right coronary artery (RCA)
Left main coronary artery (LCA)
Left circumflex coronary artery (LCX) supplies lateral and posterior walls of left ventricle, anterolateral papillary muscle
Left anterior descending artery (LAD) supplies anterior $^2/_3$ of interventricular septum, anterolateral papillary muscle, and anterior surface of left ventricle
Left (obtuse) marginal artery
Right (acute) marginal artery supplies right ventricle
Posterior descending/interventricular artery (PDA) supplies AV node, posterior $^1/_3$ of interventricular septum, posterior $^2/_3$ walls of ventricles, and posteromedial papillary muscle

SA and AV nodes are supplied by branches of the RCA. Infarct may cause nodal dysfunction (bradycardia or heart block).

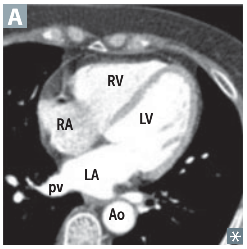
Right-dominant circulation (85%) = PDA arises from RCA.

Left-dominant circulation (8%) = PDA arises from LCX.

Codominant circulation (7%) = PDA arises from both LCX and RCA.

Coronary artery occlusion most commonly occurs in the LAD.

Coronary blood flow peaks in early diastole.


A
RV
RA
LV
LA
pv
Ao

The most posterior part of the heart is the left atrium A; enlargement can cause dysphagia (due to compression of the esophagus) or hoarseness (due to compression of the left recurrent laryngeal nerve, a branch of the vagus).

Pericardium consists of 3 layers (from outer to inner):

- Fibrous pericardium
- Parietal layer of serous pericardium
- Visceral layer of serous pericardium

Pericardial cavity lies between parietal and visceral layers.

Pericardium innervated by phrenic nerve. Pericarditis can cause referred pain to the shoulder.

▸ CARDIOVASCULAR—PHYSIOLOGY

Cardiac output	CO = stroke volume (SV) × heart rate (HR) Fick principle: $CO = \frac{\text{rate of } O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}}$ Mean arterial pressure (MAP) = CO × total peripheral resistance (TPR)	During the early stages of exercise, CO is maintained by ↑ HR and ↑ SV. During the late stages of exercise, CO is maintained by ↑ HR only (SV plateaus). Diastole is preferentially shortened with ↑ HR; less filling time → ↓ CO (eg, ventricular tachycardia).
	MAP = ⅔ diastolic pressure + ⅓ systolic pressure	
	Pulse pressure = systolic pressure – diastolic pressure Pulse pressure is proportional to SV, inversely proportional to arterial compliance. SV = end-diastolic volume (EDV) – end-systolic volume (ESV)	↑ pulse pressure in hyperthyroidism, aortic regurgitation, aortic stiffening (isolated systolic hypertension in elderly), obstructive sleep apnea (↑ sympathetic tone), exercise (transient). ↓ pulse pressure in aortic stenosis, cardiogenic shock, cardiac tamponade, advanced heart failure (HF).

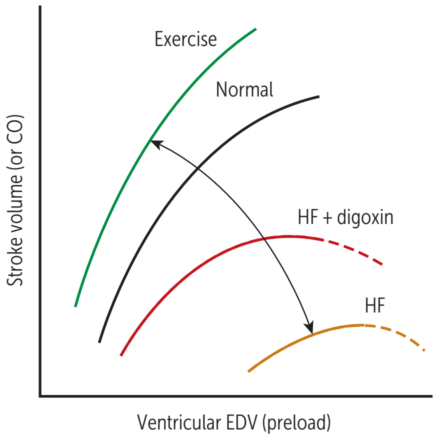
Cardiac output variables

Stroke volume	**S**troke **V**olume affected by **C**ontractility, **A**fterload, and **P**reload. ↑ SV with: ▪ ↑ Contractility (eg, anxiety, exercise) ▪ ↑ Preload (eg, early pregnancy) ▪ ↓ Afterload	**SV CAP**. A failing heart has ↓ SV (systolic and/or diastolic dysfunction)

Contractility	Contractility (and SV) ↑ with:
	▪ Catecholamine stimulation via β_1 receptor:
	  ▪ Ca^{2+} channels phosphorylated → ↑ Ca^{2+} entry → ↑ Ca^{2+}-induced Ca^{2+} release and ↑ Ca^{2+} storage in sarcoplasmic reticulum
	  ▪ Phospholamban phosphorylation → active Ca^{2+} ATPase → ↑ Ca^{2+} storage in sarcoplasmic reticulum
	▪ ↑ intracellular Ca^{2+}
	▪ ↓ extracellular Na^+ (↓ activity of Na^+/Ca^{2+} exchanger)
	▪ Digitalis (blocks Na^+/K^+ pump → ↑ intracellular Na^+ → ↓ Na^+/Ca^{2+} exchanger activity → ↑ intracellular Ca^{2+})
		Contractility (and SV) ↓ with:
		▪ β_1-blockade (↓ cAMP)
		▪ HF with systolic dysfunction
		▪ Acidosis
		▪ Hypoxia/hypercapnia (↓ P_{O_2}/↑ P_{CO_2})
		▪ Non-dihydropyridine Ca^{2+} channel blockers

Myocardial oxygen demand	Myo**CARD**ial O_2 demand is ↑ by: ▪ ↑ **C**ontractility ▪ ↑ **A**fterload (proportional to arterial pressure) ▪ ↑ heart **R**ate ▪ ↑ **D**iameter of ventricle (↑ wall tension)	Wall tension follows Laplace's law: Wall tension = pressure × radius $\text{Wall stress} = \frac{\text{pressure} \times \text{radius}}{2 \times \text{wall thickness}}$
Preload	Preload approximated by ventricular EDV; depends on venous tone and circulating blood volume.	V**E**nous vasodilators (eg, nitroglycerin) ↓ pr**E**load.
Afterload	Afterload approximated by MAP. ↑ afterload → ↑ pressure → ↑ wall tension per Laplace's law. LV compensates for ↑ afterload by thickening (hypertrophy) in order to ↓ wall tension.	**A**rterial vasodilators (eg, hydr**A**l**A**zine) ↓ **A**fterload. ACE inhibitors and ARBs ↓ both preload and afterload. Chronic hypertension (↑ MAP) → LV hypertrophy.
Ejection fraction	$\text{EF} = \frac{\text{SV}}{\text{EDV}} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}}$ Left ventricular EF is an index of ventricular contractility.	EF ↓ in systolic HF. EF normal in HF with preserved ejection fraction (HFpEF).

Starling curve



Force of contraction is proportional to end-diastolic length of cardiac muscle fiber (preload).

↑ contractility with catecholamines, positive inotropes (eg, digoxin).

↓ contractility with loss of myocardium (eg, MI), β-blockers (acutely), non-dihydropyridine Ca^{2+} channel blockers, dilated cardiomyopathy.

Resistance, pressure, flow

$\Delta P = Q \times R$

Similar to Ohm's law: $\Delta V = IR$

Volumetric flow rate (Q) = flow velocity (v) × cross-sectional area (A)

Resistance

$$= \frac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \frac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$$

Total resistance of vessels in series:

$$R_T = R_1 + R_2 + R_3 \ldots$$

Total resistance of vessels in parallel:

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} \ldots$$

Capillaries have highest total cross-sectional area and lowest flow velocity.

Pressure gradient drives flow from high pressure to low pressure.

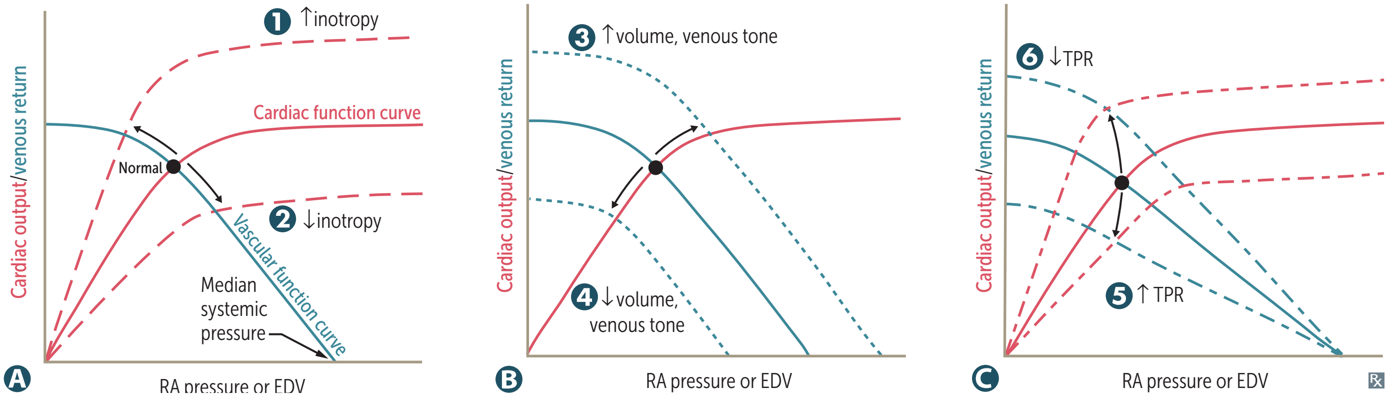
Arterioles account for most of TPR. Veins provide most of blood storage capacity.

Viscosity depends mostly on hematocrit.

Viscosity ↑ in hyperproteinemic states (eg, multiple myeloma), polycythemia.

Viscosity ↓ in anemia.

Cardiac and vascular function curves

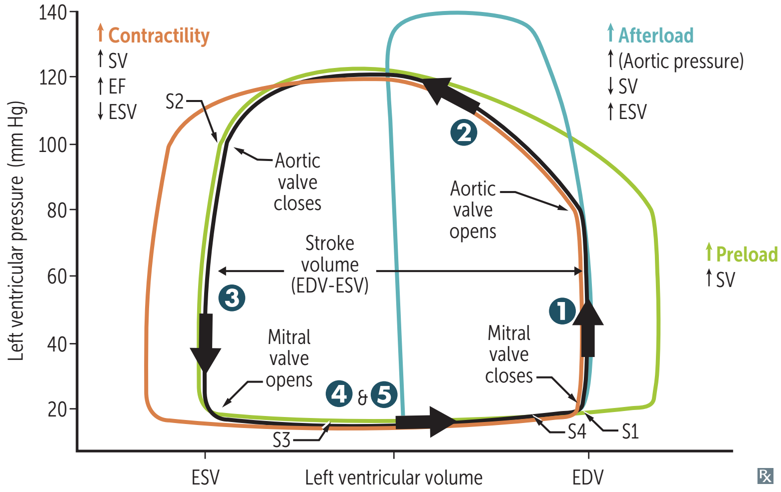


Intersection of curves = operating point of heart (ie, venous return and CO are equal).

GRAPH	EFFECT	EXAMPLES
Ⓐ Inotropy	Changes in contractility → altered CO for a given RA pressure (preload).	❶ Catecholamines, digoxin ⊕ ❷ Uncompensated HF, narcotic overdose, sympathetic inhibition ⊖
Ⓑ Venous return	Changes in circulating volume or venous tone → altered RA pressure for a given CO. Mean systemic pressure (x-intercept) changes with volume/venous tone.	❸ Fluid infusion, sympathetic activity ⊕ ❹ Acute hemorrhage, spinal anesthesia ⊖
Ⓒ Total peripheral resistance	At a given mean systemic pressure (x-intercept) and RA pressure, changes in TPR → altered CO.	❺ Vasopressors ⊕ ❻ Exercise, AV shunt ⊖

Changes often occur in tandem, and may be reinforcing (eg, exercise ↑ inotropy and ↓ TPR to maximize CO) or compensatory (eg, HF ↓ inotropy → fluid retention to ↑ preload to maintain CO).

Pressure-volume loops and cardiac cycle



The black loop represents normal cardiac physiology.

Phases—left ventricle:

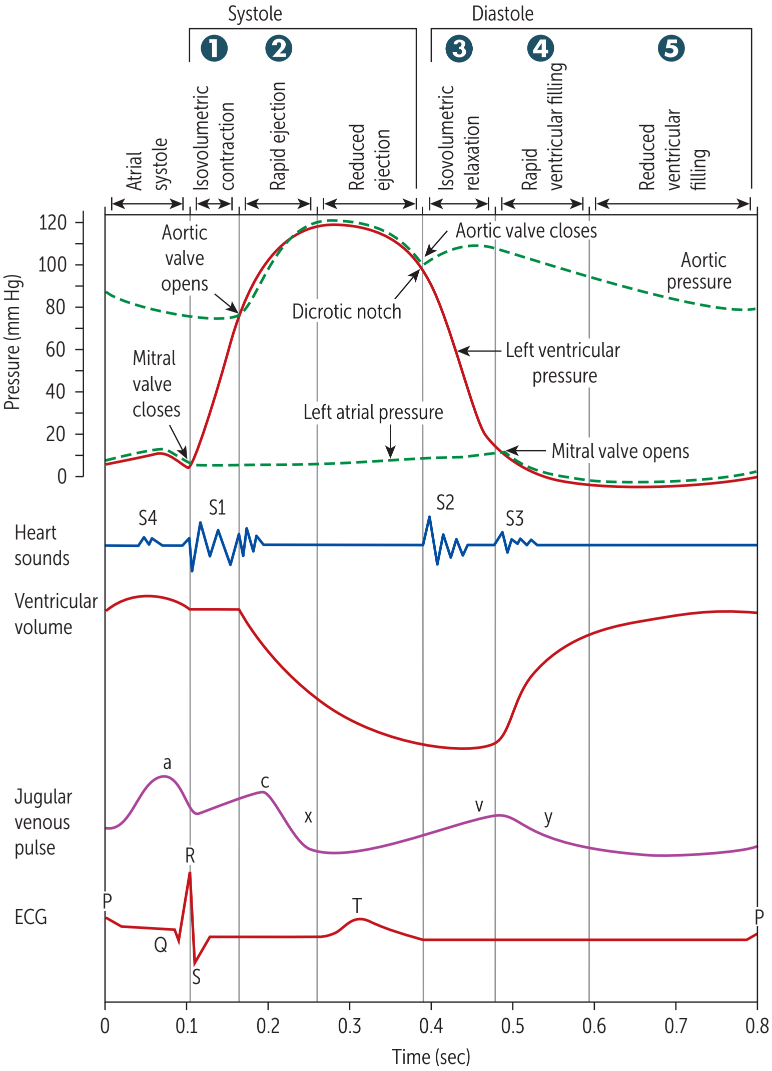
❶ Isovolumetric contraction—period between mitral valve closing and aortic valve opening; period of highest O_2 consumption

❷ Systolic ejection—period between aortic valve opening and closing

❸ Isovolumetric relaxation—period between aortic valve closing and mitral valve opening

❹ Rapid filling—period just after mitral valve opening

❺ Reduced filling—period just before mitral valve closing



Heart sounds:

S1—mitral and tricuspid valve closure. Loudest at mitral area.

S2—aortic and pulmonary valve closure. Loudest at left upper sternal border.

S3—in early diastole during rapid ventricular filling phase. Associated with ↑ filling pressures (eg, mitral regurgitation, HF) and more common in dilated ventricles (but can be normal in children and young adults).

S4—in late diastole ("atrial kick"). Best heard at apex with patient in left lateral decubitus position. High atrial pressure. Associated with ventricular noncompliance (eg, hypertrophy). Left atrium must push against stiff LV wall. Consider abnormal, regardless of patient age.

Jugular venous pulse (JVP):

a wave—atrial contraction. Absent in atrial fibrillation (AF).

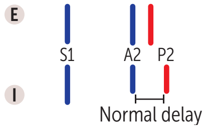
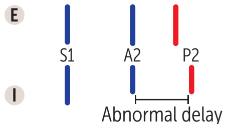
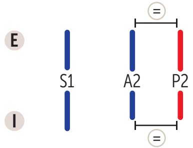
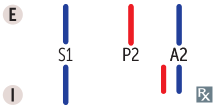
c wave—RV contraction (closed tricuspid valve bulging into atrium).

x descent—downward displacement of closed tricuspid valve during rapid ventricular ejection phase. Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced.

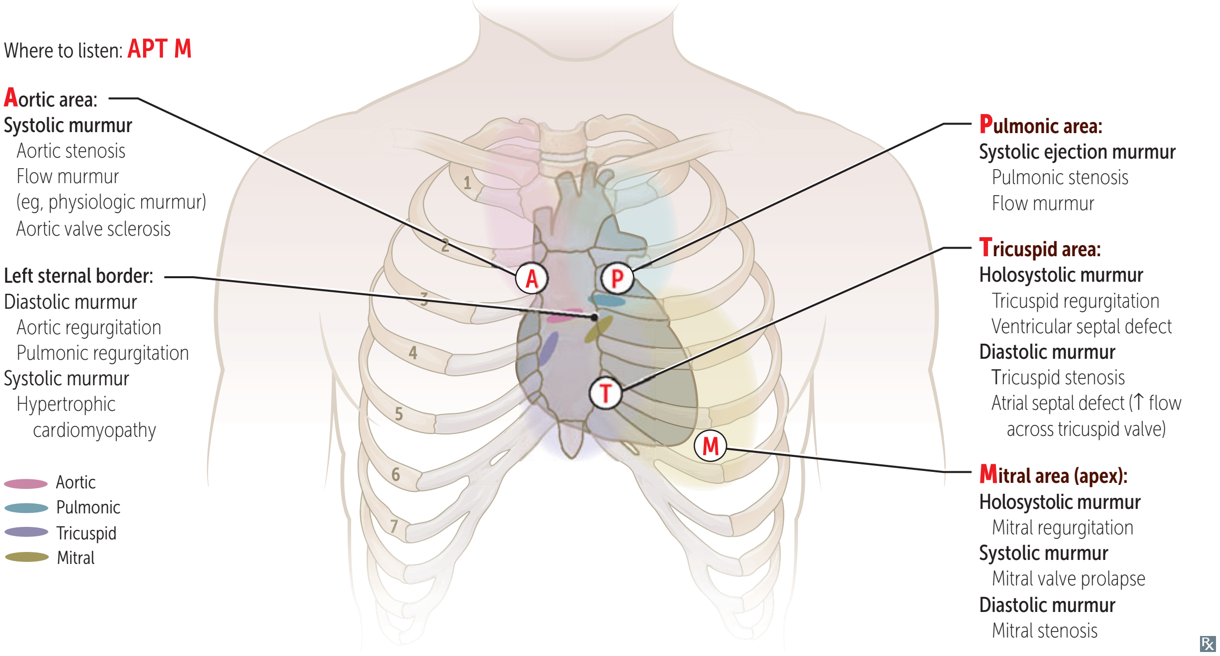
v wave—↑ right atrial pressure due to filling ("villing") against closed tricuspid valve.

y descent—RA emptying into RV. Prominent in constrictive pericarditis, absent in cardiac tamponade.

Splitting

Normal splitting	Inspiration → drop in intrathoracic pressure → ↑ venous return → ↑ RV filling → ↑ RV stroke volume → ↑ RV ejection time → delayed closure of pulmonic valve. ↓ pulmonary impedance (↑ capacity of the pulmonary circulation) also occurs during inspiration, which contributes to delayed closure of pulmonic valve.	
Wide splitting	Seen in conditions that delay RV emptying (eg, pulmonic stenosis, right bundle branch block). Causes delayed pulmonic sound (especially on inspiration). An exaggeration of normal splitting.	
Fixed splitting	Heard in ASD. ASD → left-to-right shunt → ↑ RA and RV volumes → ↑ flow through pulmonic valve such that, regardless of breath, pulmonic closure is greatly delayed.	
Paradoxical splitting	Heard in conditions that delay aortic valve closure (eg, aortic stenosis, left bundle branch block). Normal order of valve closure is reversed so that P2 sound occurs before delayed A2 sound. Therefore on inspiration, P2 closes later and moves closer to A2, thereby "paradoxically" eliminating the split (usually heard in expiration).	 E = Expiration I = Inspiration

Auscultation of the heart


Where to listen: APT M
Aortic area:
Systolic murmur
Aortic stenosis
Flow murmur
(eg, physiologic murmur)
Aortic valve sclerosis
Left sternal border:
Diastolic murmur
Aortic regurgitation
Pulmonic regurgitation
Systolic murmur
Hypertrophic cardiomyopathy
🟥 Aortic
🟦 Pulmonic
🟪 Tricuspid
🟨 Mitral
1
2
3
4
5
6
7
A
P
T
M
Pulmonic area:
Systolic ejection murmur
Pulmonic stenosis
Flow murmur
Tricuspid area:
Holosystolic murmur
Tricuspid regurgitation
Ventricular septal defect
Diastolic murmur
Tricuspid stenosis
Atrial septal defect (↑ flow across tricuspid valve)
Mitral area (apex):
Holosystolic murmur
Mitral regurgitation
Systolic murmur
Mitral valve prolapse
Diastolic murmur
Mitral stenosis

BEDSIDE MANEUVER	EFFECT
Inspiration (↑ venous return to right atrium)	↑ intensity of right heart sounds
Hand grip (↑ afterload)	↑ intensity of MR, AR, and VSD murmurs ↓ hypertrophic cardiomyopathy and AS murmurs MVP: later onset of click/murmur
Valsalva (phase II), standing up (↓ preload)	↓ intensity of most murmurs (including AS) ↑ intensity of hypertrophic cardiomyopathy murmur MVP: earlier onset of click/murmur
Rapid squatting (↑ venous return, ↑ preload, ↑ afterload)	↓ intensity of hypertrophic cardiomyopathy murmur ↑ intensity of AS, MR, and VSD murmurs MVP: later onset of click/murmur

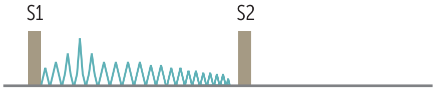
Systolic heart sounds include the murmurs of aortic/pulmonic stenosis, mitral/tricuspid regurgitation, VSD, MVP, hypertrophic cardiomyopathy.

Diastolic heart sounds include the murmurs of aortic/pulmonic regurgitation, mitral/tricuspid stenosis.

Heart murmurs

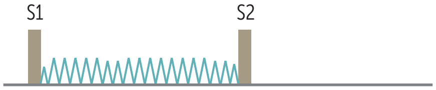
Systolic

Aortic stenosis



Crescendo-decrescendo systolic ejection murmur (ejection click may be present). LV >> aortic pressure during systole. Loudest at heart base; radiates to carotids. "Pulsus parvus et tardus"—pulses are weak with a delayed peak. Can lead to **S**yncope, **A**ngina, and **D**yspnea on exertion (**SAD**). Most commonly due to age-related calcification in older patients (> 60 years old) or in younger patients with early-onset calcification of bicuspid aortic valve.

Mitral/tricuspid regurgitation



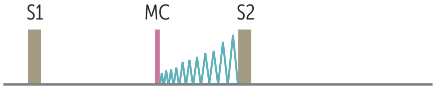
Holosystolic, high-pitched "blowing murmur."

Mitral—loudest at apex and radiates toward axilla. MR is often due to ischemic heart disease (post-MI), MVP, LV dilatation.

Tricuspid—loudest at tricuspid area. TR commonly caused by RV dilatation.

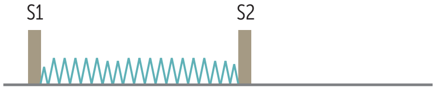
Rheumatic fever and infective endocarditis can cause either MR or TR.

Mitral valve prolapse



Late systolic crescendo murmur with midsystolic click (MC; due to sudden tensing of chordae tendineae). Most frequent valvular lesion. Best heard over apex. Loudest just before S2. Usually benign. Can predispose to infective endocarditis. Can be caused by myxomatous degeneration (1° or 2° to connective tissue disease such as Marfan or Ehlers-Danlos syndrome), rheumatic fever, chordae rupture.

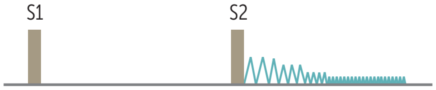
Ventricular septal defect



Holosystolic, harsh-sounding murmur. Loudest at tricuspid area.

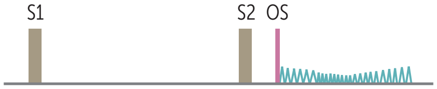
Diastolic

Aortic regurgitation



High-pitched "blowing" early diastolic decrescendo murmur. Long diastolic murmur, hyperdynamic pulse, and head bobbing when severe and chronic. Wide pulse pressure. Often due to aortic root dilation, bicuspid aortic valve, endocarditis, rheumatic fever. Progresses to left HF.

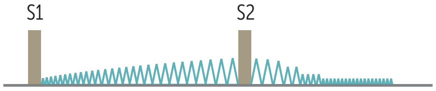
Mitral stenosis



Follows opening snap (OS; due to abrupt halt in leaflet motion in diastole, after rapid opening due to fusion at leaflet tips). Delayed rumbling mid-to-late diastolic murmur (↓ interval between S2 and OS correlates with ↑ severity). LA >> LV pressure during diastole. Often a late (and highly specific) sequela of rheumatic fever. Chronic MS can result in LA dilatation.

Continuous

Patent ductus arteriosus



Continuous machine-like murmur. Loudest at S2. Often due to congenital rubella or prematurity. Best heard at left infraclavicular area.

Myocardial action potential

Also occurs in bundle of His and Purkinje fibers.

Phase 0 = rapid upstroke and depolarization—voltage-gated Na^+ channels open.

Phase 1 = initial repolarization—inactivation of voltage-gated Na^+ channels. Voltage-gated K^+ channels begin to open.

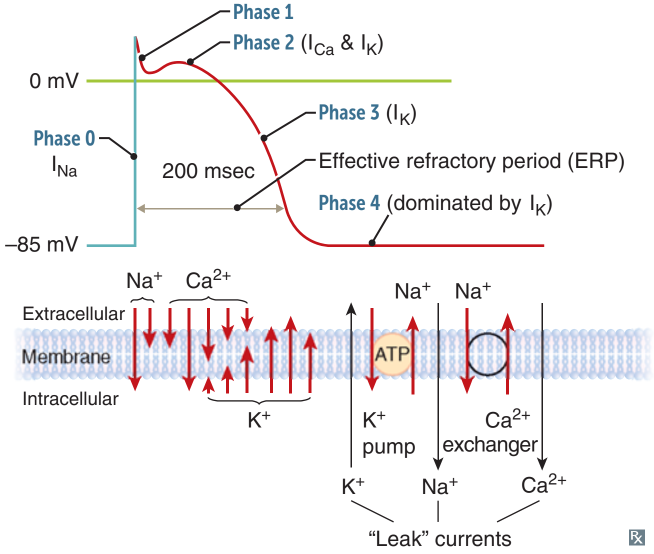
Phase 2 = plateau—Ca^{2+} influx through voltage-gated Ca^{2+} channels balances K^+ efflux. Ca^{2+} influx triggers Ca^{2+} release from sarcoplasmic reticulum and myocyte contraction.

Phase 3 = rapid repolarization—massive K^+ efflux due to opening of voltage-gated slow K^+ channels and closure of voltage-gated Ca^{2+} channels.

Phase 4 = resting potential—high K^+ permeability through K^+ channels.

In contrast to skeletal muscle:

- Cardiac muscle action potential has a plateau, which is due to Ca^{2+} influx and K^+ efflux.
- Cardiac muscle contraction requires Ca^{2+} influx from ECF to induce Ca^{2+} release from sarcoplasmic reticulum (Ca^{2+}-induced Ca^{2+} release).
- Cardiac myocytes are electrically coupled to each other by gap junctions.


Phase 1
Phase 2 (I_{Ca} & I_K)
0 mV
Phase 3 (I_K)
Phase 0
I_{Na}
200 msec
Effective refractory period (ERP)
Phase 4 (dominated by I_K)
–85 mV
Na^+
Ca^{2+}
Extracellular
Membrane
Intracellular
K^+
Na^+
Na^+
ATP
K^+ pump
Ca^{2+} exchanger
K^+
Na^+
Ca^{2+}
"Leak" currents

Pacemaker action potential

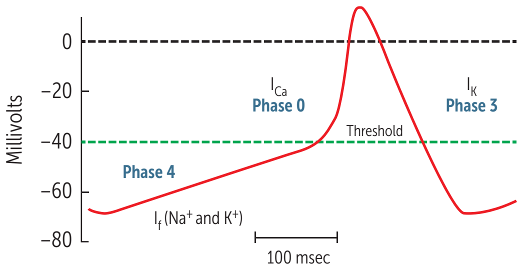
Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

Phase 0 = upstroke—opening of voltage-gated Ca^{2+} channels. Fast voltage-gated Na^+ channels are permanently inactivated because of the less negative resting potential of these cells. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles.

Phases 1 and 2 are absent.

Phase 3 = inactivation of the Ca^{2+} channels and ↑ activation of K^+ channels → ↑ K^+ efflux.

Phase 4 = slow spontaneous diastolic depolarization due to I_f ("funny current"). I_f channels responsible for a slow, mixed Na^+/K^+ inward current; different from I_{Na} in phase 0 of ventricular action potential. Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines HR. ACh/adenosine ↓ the rate of diastolic depolarization and ↓ HR, while catecholamines ↑ depolarization and ↑ HR. Sympathetic stimulation ↑ the chance that I_f channels are open and thus ↑ HR.



Electrocardiogram

Conduction pathway—SA node → atria → AV node → bundle of His → right and left bundle branches → Purkinje fibers → ventricles; left bundle branch divides into left anterior and posterior fascicles.

SA node "pacemaker" inherent dominance with slow phase of upstroke.

AV node—located in posteroinferior part of interatrial septum. Blood supply usually from RCA. 100-msec delay allows time for ventricular filling.

Pacemaker rates—SA > AV > bundle of His/Purkinje/ventricles.

Speed of conduction—Purkinje > atria > ventricles > AV node.

P wave—atrial depolarization. Atrial repolarization is masked by QRS complex.

PR interval—time from start of atrial depolarization to start of ventricular depolarization (normally < 200 msec).

QRS complex—ventricular depolarization (normally < 120 msec).

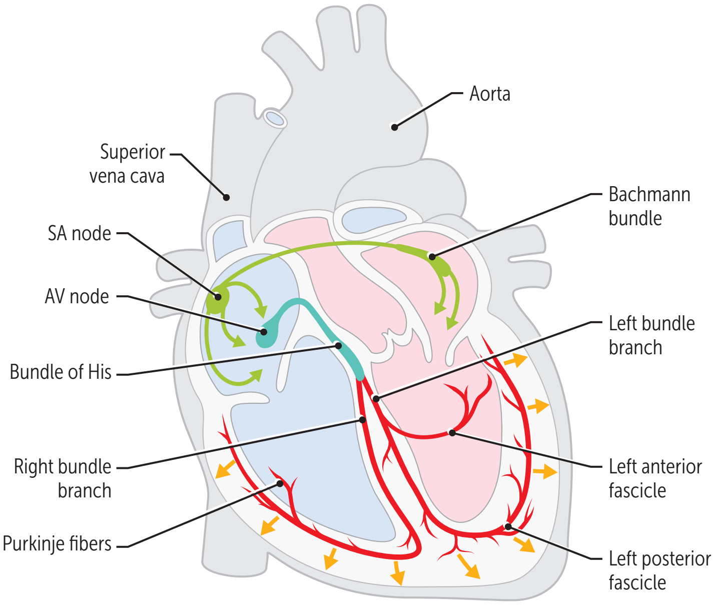
QT interval—ventricular depolarization, mechanical contraction of the ventricles, ventricular repolarization.

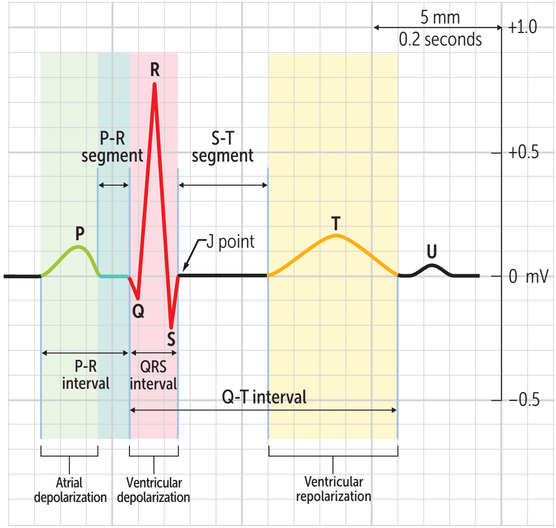
T wave—ventricular repolarization. T-wave inversion may indicate ischemia or recent MI.

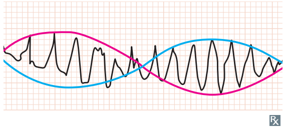
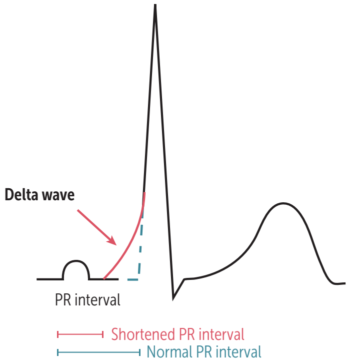
J point—junction between end of QRS complex and start of ST segment.

ST segment—isoelectric, ventricles depolarized.

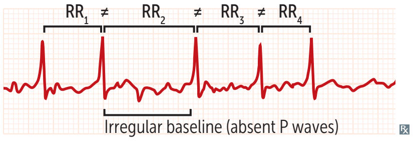
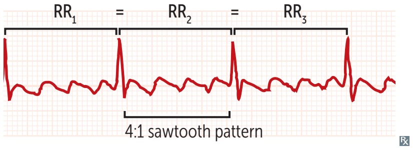
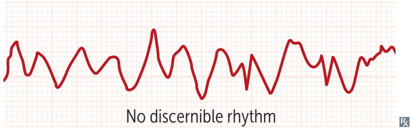
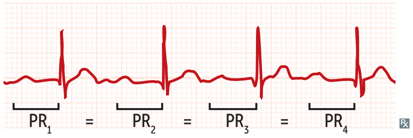
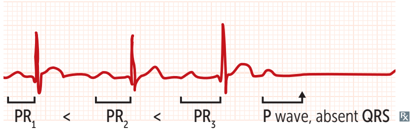
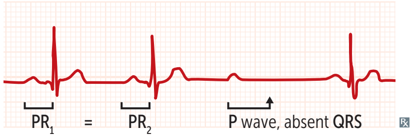
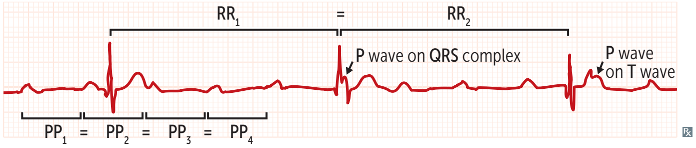
U wave—prominent in hypokalemia, bradycardia.


Aorta
Superior vena cava
SA node
AV node
Bundle of His
Right bundle branch
Purkinje fibers
Bachmann bundle
Left bundle branch
Left anterior fascicle
Left posterior fascicle


5 mm
0.2 seconds
+1.0
+0.5
0 mV
−0.5
R
P-R segment
S-T segment
P
T
U
J point
Q
S
P-R interval
QRS interval
Q-T interval
Atrial depolarization
Ventricular depolarization
Ventricular repolarization

Torsades de pointes 	Polymorphic ventricular tachycardia, characterized by shifting sinusoidal waveforms on ECG; can progress to ventricular fibrillation (VF). Long QT interval predisposes to torsades de pointes. Caused by drugs, ↓ K^+, ↓ Mg^{2+}, congenital abnormalities. Treatment includes magnesium sulfate.	Drug-induced long QT (**ABCDE**): Anti**A**rrhythmics (class IA, III) Anti**B**iotics (eg, macrolides) Anti"**C**"ychotics (eg, haloperidol) Anti**D**epressants (eg, TCAs) Anti**E**metics (eg, ondansetron) Torsades de pointes = twisting of the points
Congenital long QT syndrome	Inherited disorder of myocardial repolarization, typically due to ion channel defects; ↑ risk of sudden cardiac death (SCD) due to torsades de pointes. Includes: ▪ **Romano-Ward syndrome**—autosomal dominant, pure cardiac phenotype (no deafness). ▪ **Jervell and Lange-Nielsen syndrome**—autosomal recessive, sensorineural deafness.	
Brugada syndrome	Autosomal dominant disorder most common in Asian males. ECG pattern of pseudo-right bundle branch block and ST elevations in V_1-V_3. ↑ risk of ventricular tachyarrhythmias and SCD. Prevent SCD with implantable cardioverter-defibrillator (ICD).	
Wolff-Parkinson-White syndrome	Most common type of ventricular pre-excitation syndrome. Abnormal fast accessory conduction pathway from atria to ventricle (bundle of Kent) bypasses the rate-slowing AV node → ventricles begin to partially depolarize earlier → characteristic delta wave with widened QRS complex and shortened PR interval on ECG. May result in reentry circuit → supraventricular tachycardia.	 Delta wave PR interval Shortened PR interval Normal PR interval

ECG tracings

RHYTHM	DESCRIPTION	EXAMPLE
Atrial fibrillation	Chaotic and erratic baseline with no discrete P waves in between irregularly spaced QRS complexes. Irregularly irregular heartbeat. Most common risk factors include hypertension and coronary artery disease (CAD). Can lead to thromboembolic events, particularly stroke. Treatment includes anticoagulation, rate control, rhythm control, and/or cardioversion.	 $RR_1 \neq RR_2 \neq RR_3 \neq RR_4$ Irregular baseline (absent P waves)
Atrial flutter	A rapid succession of identical, back-to-back atrial depolarization waves. The identical appearance accounts for the "sawtooth" appearance of the flutter waves. Treat like atrial fibrillation. Definitive treatment is catheter ablation.	 $RR_1 = RR_2 = RR_3$ 4:1 sawtooth pattern
Ventricular fibrillation	A completely erratic rhythm with no identifiable waves. Fatal arrhythmia without immediate CPR and defibrillation.	 No discernible rhythm
AV block		
First degree	The PR interval is prolonged (> 200 msec). Benign and asymptomatic. No treatment required.	 $PR_1 = PR_2 = PR_3 = PR_4$
Second degree		
Mobitz type I (Wenckebach)	Progressive lengthening of PR interval until a beat is "dropped" (a P wave not followed by a QRS complex). Usually asymptomatic. Variable RR interval with a pattern (regularly irregular).	 $PR_1 < PR_2 < PR_3$ P wave, absent QRS
Mobitz type II	Dropped beats that are not preceded by a change in the length of the PR interval (as in type I). May progress to 3rd-degree block. Often treated with pacemaker.	 $PR_1 = PR_2$ P wave, absent QRS
Third degree (complete)	The atria and ventricles beat independently of each other. P waves and QRS complexes not rhythmically associated. Atrial rate > ventricular rate. Usually treated with pacemaker. Can be caused by Lyme disease.	 $RR_1 = RR_2$ P wave on QRS complex P wave on T wave $PP_1 = PP_2 = PP_3 = PP_4$

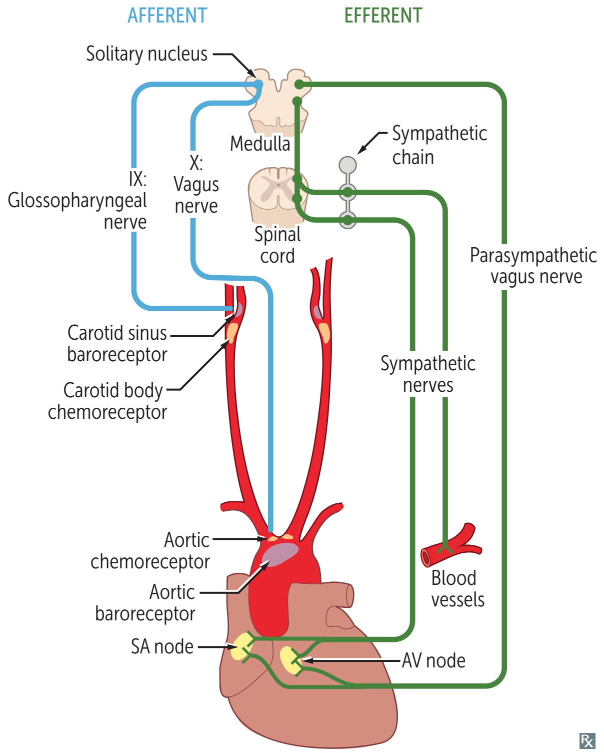
Atrial natriuretic peptide

Released from **atrial myocytes** in response to ↑ blood volume and atrial pressure. Acts via cGMP. Causes vasodilation and ↓ Na^+ reabsorption at the renal collecting tubule. Dilates afferent renal arterioles and constricts efferent arterioles, promoting diuresis and contributing to "aldosterone escape" mechanism.

B-type (brain) natriuretic peptide

Released from **ventricular myocytes** in response to ↑ tension. Similar physiologic action to ANP, with longer half-life. BNP blood test used for diagnosing HF (very good negative predictive value). Available in recombinant form (nesiritide) for treatment of HF.

Baroreceptors and chemoreceptors


AFFERENT
EFFERENT
Solitary nucleus
Medulla
IX: Glossopharyngeal nerve
X: Vagus nerve
Spinal cord
Sympathetic chain
Parasympathetic vagus nerve
Carotid sinus baroreceptor
Carotid body chemoreceptor
Sympathetic nerves
Aortic chemoreceptor
Aortic baroreceptor
SA node
AV node
Blood vessels

Receptors:

- Aortic arch transmits via vagus nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).
- Carotid sinus (dilated region at carotid bifurcation) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to ↓ and ↑ in BP).

Baroreceptors:

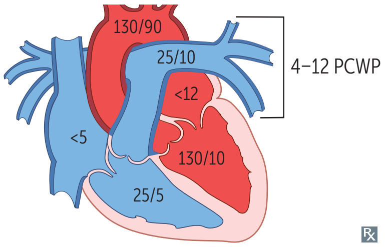
- Hypotension—↓ arterial pressure → ↓ stretch → ↓ afferent baroreceptor firing → ↑ efferent sympathetic firing and ↓ efferent parasympathetic stimulation → vasoconstriction, ↑ HR, ↑ contractility, ↑ BP. Important in the response to severe hemorrhage.
  - Carotid massage—↑ pressure on carotid sinus → ↑ stretch → ↑ afferent baroreceptor firing → ↑ AV node refractory period → ↓ HR.
  - Component of Cushing reflex (triad of hypertension, bradycardia, and respiratory depression)—↑ intracranial pressure constricts arterioles → cerebral ischemia → ↑ pCO_2 and ↓ pH → central reflex sympathetic ↑ in perfusion pressure (hypertension) → ↑ stretch → peripheral reflex baroreceptor–induced bradycardia.

Chemoreceptors:

- Peripheral—carotid and aortic bodies are stimulated by ↓ P_{O_2} (< 60 mm Hg), ↑ P_{CO_2}, and ↓ pH of blood.
- Central—are stimulated by changes in pH and P_{CO_2} of brain interstitial fluid, which in turn are influenced by arterial CO_2. Do not directly respond to P_{O_2}.

Normal cardiac pressures

Pulmonary capillary wedge pressure (PCWP; in mm Hg) is a good approximation of left atrial pressure. In mitral stenosis, PCWP > LV end diastolic pressure. PCWP is measured with pulmonary artery catheter (Swan-Ganz catheter).

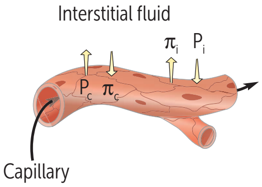


Autoregulation

How blood flow to an organ remains constant over a wide range of perfusion pressures.

ORGAN	FACTORS DETERMINING AUTOREGULATION	
Heart	Local metabolites (vasodilatory): adenosine, NO, CO_2, ↓ O_2	Note: the pulmonary vasculature is unique in that hypoxia causes vasoconstriction so that only well-ventilated areas are perfused. In other organs, hypoxia causes vasodilation.
Brain	Local metabolites (vasodilatory): CO_2 (pH)	
Kidneys	Myogenic and tubuloglomerular feedback	
Lungs	Hypoxia causes vasoconstriction	
Skeletal muscle	Local metabolites during exercise: lactate, adenosine, K^+, H^+, CO_2 At rest: sympathetic tone	**C**O_2, **H**$^+$, **A**denosine, **L**actate, **K**$^+$ (**CHALK**)
Skin	Sympathetic stimulation most important mechanism for temperature control	

Capillary fluid exchange



Starling forces determine fluid movement through capillary membranes:

- P_c = capillary pressure—pushes fluid out of capillary
- P_i = interstitial fluid pressure—pushes fluid into capillary
- π_c = plasma colloid osmotic (oncotic) pressure—pulls fluid into capillary
- π_i = interstitial fluid colloid osmotic pressure—pulls fluid out of capillary

J_v = net fluid flow = $K_f\,[(P_c - P_i) - \varsigma(\pi_c - \pi_i)]$

K_f = capillary permeability to fluid

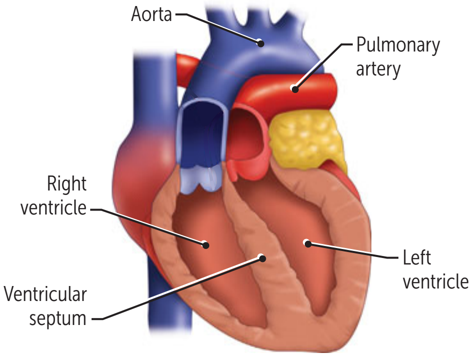
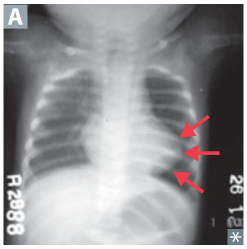
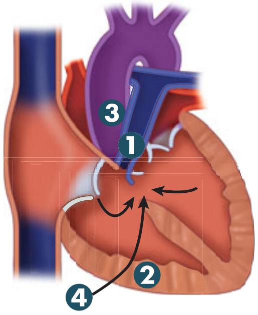
ς = reflection coefficient (measure of capillary permeability to protein)

Edema—excess fluid outflow into interstitium commonly caused by:

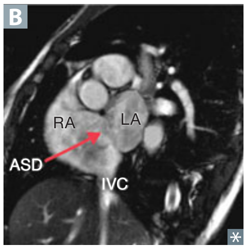
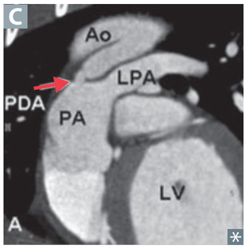
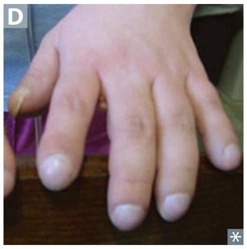
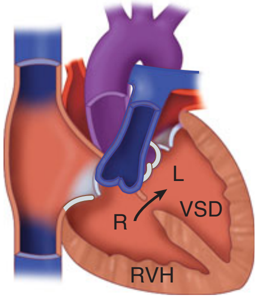
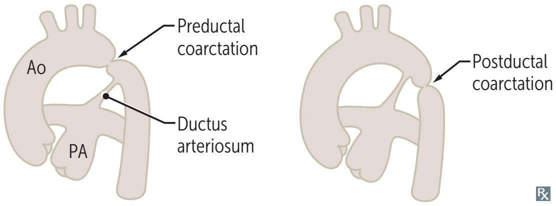
- ↑ capillary pressure (↑ P_c; eg, HF)
- ↓ plasma proteins (↓ π_c; eg, nephrotic syndrome, liver failure, protein malnutrition)
- ↑ capillary permeability (↑ K_f; eg, toxins, infections, burns)
- ↑ interstitial fluid colloid osmotic pressure (↑ π_i; eg, lymphatic blockage)

▸ CARDIOVASCULAR—PATHOLOGY

Congenital heart diseases

RIGHT-TO-LEFT SHUNTS	Early cyanosis—"blue babies." Often diagnosed prenatally or become evident immediately after birth. Usually require urgent surgical treatment and/or maintenance of a PDA.	The 5 Ts: 1. Truncus arteriosus (1 vessel) 2. Transposition (2 switched vessels) 3. Tricuspid atresia (3 = Tri) 4. Tetralogy of Fallot (4 = Tetra) 5. TAPVR (5 letters in the name)
Persistent truncus arteriosus	Truncus arteriosus fails to divide into pulmonary trunk and aorta due to lack of aorticopulmonary septum formation; most patients have accompanying VSD.	
D-transposition of great vessels	Aorta leaves RV (anterior) and pulmonary trunk leaves LV (posterior) → separation of systemic and pulmonary circulations. Not compatible with life unless a shunt is present to allow mixing of blood (eg, VSD, PDA, or patent foramen ovale). Due to failure of the aorticopulmonary septum to spiral. Without surgical intervention, most infants die within the first few months of life.	 Aorta Pulmonary artery Right ventricle Left ventricle Ventricular septum
Tricuspid atresia	Absence of tricuspid valve and hypoplastic RV; requires both ASD and VSD for viability.	
Tetralogy of Fallot 	Caused by anterosuperior displacement of the infundibular septum. Most common cause of early childhood cyanosis. ① Pulmonary infundibular stenosis (most important determinant for prognosis) ② Right ventricular hypertrophy (RVH)—boot-shaped heart on CXR A ③ Overriding aorta ④ VSD Pulmonary stenosis forces right-to-left flow across VSD → RVH, "tet spells" (often caused by crying, fever, and exercise due to exacerbation of RV outflow obstruction).	PROVe. Squatting: ↑ SVR, ↓ right-to-left shunt, improves cyanosis. Treatment: early surgical correction. 
Total anomalous pulmonary venous return	Pulmonary veins drain into right heart circulation (SVC, coronary sinus, etc); associated with ASD and sometimes PDA to allow for right-to-left shunting to maintain CO.	
Ebstein anomaly	Characterized by displacement of tricuspid valve leaflets downward into RV, artificially "atrializing" the ventricle. Associated with tricuspid regurgitation and right HF. Can be caused by lithium exposure in utero.	

Congenital heart diseases *(continued)*

LEFT-TO-RIGHT SHUNTS	Acyanotic at presentation; cyanosis may occur years later. Frequency: VSD > ASD > PDA.	**R**ight-to-**L**eft shunts: ea**RL**y cyanosis. **L**eft-to-**R**ight shunts: "**L**ate**R**" cyanosis.
Ventricular septal defect	Most common congenital cardiac defect. Asymptomatic at birth, may manifest weeks later or remain asymptomatic throughout life. Most self resolve; larger lesions may lead to LV overload and HF.	O_2 saturation ↑ in RV and pulmonary artery.
Atrial septal defect 	Defect in interatrial septum B; loud S1; wide, fixed split S2. Ostium secundum defects most common and usually occur as isolated findings; ostium primum defects rarer yet usually occur with other cardiac anomalies. Symptoms range from none to HF. Distinct from patent foramen ovale in that septa are missing tissue rather than unfused.	O_2 saturation ↑ in RA, RV, and pulmonary artery. May lead to paradoxical emboli (systemic venous emboli use ASD to bypass lungs and become systemic arterial emboli).
Patent ductus arteriosus 	In fetal period, shunt is right to left (normal). In neonatal period, ↓ pulmonary vascular resistance → shunt becomes left to right → progressive RVH and/or LVH and HF. Associated with a continuous, "machine-like" murmur. Patency is maintained by PGE synthesis and low O_2 tension. Uncorrected PDA C can eventually result in late cyanosis in the lower extremities (differential cyanosis).	"**End**omethacin" (indomethacin) **end**s patency of PDA; P**G**E keeps ductus **G**oing (may be necessary to sustain life in conditions such as transposition of the great vessels). PDA is normal in utero and normally closes only after birth.
Eisenmenger syndrome 	Uncorrected left-to-right shunt (VSD, ASD, PDA) → ↑ pulmonary blood flow → pathologic remodeling of vasculature → pulmonary arterial hypertension. RVH occurs to compensate → shunt becomes right to left. Causes late cyanosis, clubbing D, and polycythemia. Age of onset varies.	
OTHER ANOMALIES		
Coarctation of the aorta	Aortic narrowing near insertion of ductus arteriosus ("juxtaductal"). Associated with bicuspid aortic valve, other heart defects, and Turner syndrome. Hypertension in upper extremities and weak, delayed pulse in lower extremities (brachial-femoral delay). With age, intercostal arteries enlarge due to collateral circulation; arteries erode ribs → notched appearance on CXR. Complications include HF, ↑ risk of cerebral hemorrhage (berry aneurysms), aortic rupture, and possible endocarditis.	 Ao Preductal coarctation Ductus arteriosum PA Postductal coarctation

Congenital cardiac defect associations

DISORDER	DEFECT
Alcohol exposure in utero (fetal alcohol syndrome)	VSD, PDA, ASD, tetralogy of Fallot
Congenital rubella	PDA, pulmonary artery stenosis, septal defects
Down syndrome	AV septal defect (endocardial cushion defect), VSD, ASD
Infant of diabetic mother	Transposition of great vessels
Marfan syndrome	MVP, thoracic aortic aneurysm and dissection, aortic regurgitation
Prenatal lithium exposure	Ebstein anomaly
Turner syndrome	Bicuspid aortic valve, coarctation of aorta
Williams syndrome	Supravalvular aortic stenosis
22q11 syndromes	Truncus arteriosus, tetralogy of Fallot

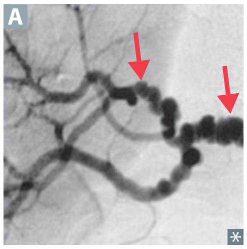
Hypertension

Defined as persistent systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg

RISK FACTORS

↑ age, obesity, diabetes, physical inactivity, excess salt intake, excess alcohol intake, family history; African American > Caucasian > Asian.

FEATURES



90% of hypertension is 1° (essential) and related to ↑ CO or ↑ TPR. Remaining 10% mostly 2° to renal/renovascular disease (eg, fibromuscular dysplasia [which has characteristic "string of beads" appearance of renal artery A], atherosclerosis) and 1° hyperaldosteronism.

Hypertensive urgency—severe (≥ 180/≥ 120 mm Hg) hypertension without acute end-organ damage.

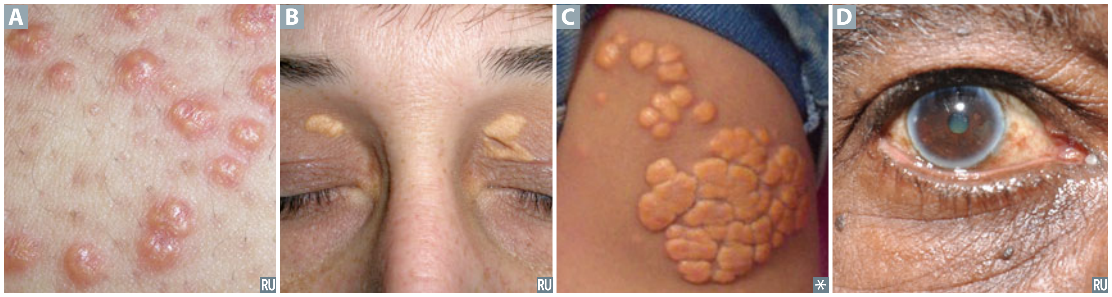
Hypertensive emergency—severe hypertension with evidence of acute end-organ damage (eg, encephalopathy, stroke, retinal hemorrhages and exudates, papilledema, MI, HF, aortic dissection, kidney injury, microangiopathic hemolytic anemia, eclampsia).

PREDISPOSES TO

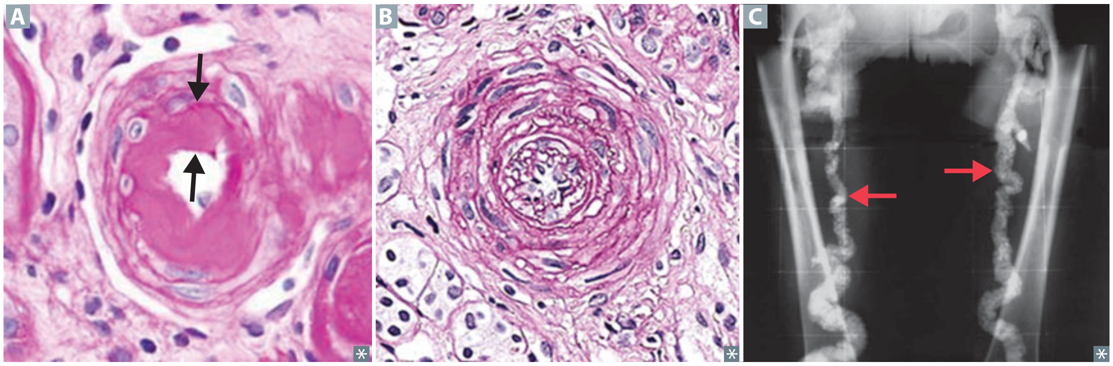
CAD, LVH, HF, atrial fibrillation; aortic dissection, aortic aneurysm; stroke; chronic kidney disease (hypertensive nephropathy); retinopathy.

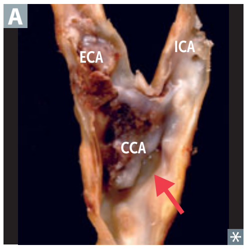
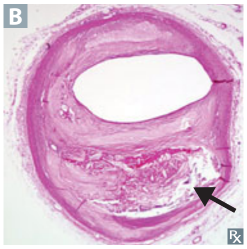
Hyperlipidemia signs

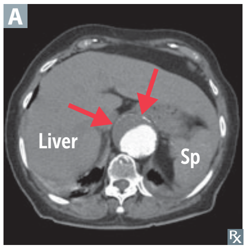
Xanthomas	Plaques or nodules composed of lipid-laden histiocytes in skin A, especially the eyelids (xanthelasma B).
Tendinous xanthoma	Lipid deposit in tendon C, especially Achilles.
Corneal arcus	Lipid deposit in cornea. Common in elderly (arcus senilis D), but appears earlier in life in hypercholesterolemia.



Arteriosclerosis	Hardening of arteries, with arterial wall thickening and loss of elasticity.
Arteriolosclerosis	Common. Affects small arteries and arterioles. Two types: hyaline (thickening of vessel walls in essential hypertension or diabetes mellitus A) and hyperplastic ("onion skinning" in severe hypertension B with proliferation of smooth muscle cells).
Mönckeberg sclerosis (medial calcific sclerosis)	Uncommon. Affects medium-sized arteries. Calcification of internal elastic lamina and media of arteries → vascular stiffening without obstruction. "Pipestem" appearance on x-ray C. Does not obstruct blood flow; intima not involved.

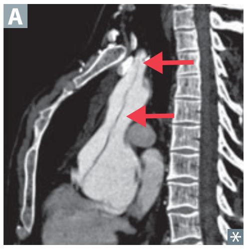


Atherosclerosis	Very common. Disease of elastic arteries and large- and medium-sized muscular arteries; a form of arteriosclerosis caused by buildup of cholesterol plaques.
LOCATION 	Abdominal aorta > coronary artery > popliteal artery > carotid artery A.
RISK FACTORS	Modifiable: smoking, hypertension, hyperlipidemia (↑ LDL), diabetes. Nonmodifiable: age, sex (↑ in men and postmenopausal women), family history.
SYMPTOMS	Angina, claudication, but can be asymptomatic.
PROGRESSION 	Inflammation important in pathogenesis: endothelial cell dysfunction → macrophage and LDL accumulation → foam cell formation → fatty streaks → smooth muscle cell migration (involves PDGF and FGF), proliferation, and extracellular matrix deposition → fibrous plaque → complex atheromas B.
COMPLICATIONS	Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.

Aortic aneurysm	Localized pathologic dilatation of the aorta. May cause abdominal and/or back pain, which is a sign of leaking, dissection, or imminent rupture.
Abdominal aortic aneurysm 	Associated with atherosclerosis. Risk factors include history of tobacco use, ↑ age, male sex, family history. May present as palpable pulsatile abdominal mass (arrows in A point to outer dilated calcified aortic wall, with partial crescent-shaped nonopacification of aorta due to flap/clot).
Thoracic aortic aneurysm	Associated with cystic medial degeneration. Risk factors include hypertension, bicuspid aortic valve, connective tissue disease (eg, Marfan syndrome). Also historically associated with 3° syphilis (obliterative endarteritis of the vasa vasorum). Aortic root dilatation may lead to aortic valve regurgitation.

Traumatic aortic rupture	Due to trauma and/or deceleration injury, most commonly at aortic isthmus (proximal descending aorta just distal to origin of left subclavian artery).

Aortic dissection



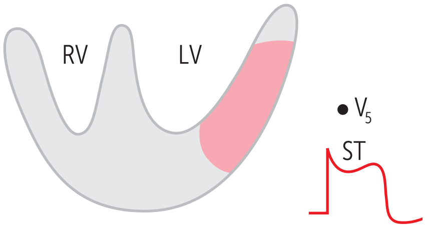
Longitudinal intimal tear forming a false lumen (arrows in A show flap extending into ascending aorta, Stanford type A dissection). Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (eg, Marfan syndrome). Can present with tearing, sudden-onset chest pain, radiating to the back +/– markedly unequal BP in arms. CXR shows mediastinal widening. Can result in organ ischemia, aortic rupture, death. Two types:

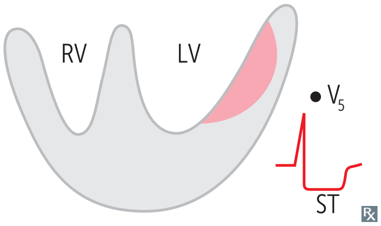
- Stanford type **A** (proximal): involves **A**scending aorta. May extend to aortic arch or descending aorta. May result in acute aortic regurgitation or cardiac tamponade. Treatment: surgery.
- Stanford type **B** (distal): only involves descending aorta (**B**elow ligamentum arteriosum). Treat medically with β-blockers, then vasodilators.

Ischemic heart disease manifestations

Angina	Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no myocyte necrosis. ▪ Stable—usually 2° to atherosclerosis; exertional chest pain in classic distribution (usually with ST depression on ECG), resolving with rest or nitroglycerin. ▪ Variant (Prinzmetal)—occurs at rest 2° to coronary artery spasm; transient ST elevation on ECG. Smoking is a risk factor, but hypertension and hypercholesterolemia are not. Triggers may include cocaine, alcohol, and triptans. Treat with Ca^{2+} channel blockers, nitrates, and smoking cessation (if applicable). ▪ Unstable—thrombosis with incomplete coronary artery occlusion; +/– ST depression and/or T-wave inversion on ECG but no cardiac biomarker elevation (unlike NSTEMI); ↑ in frequency or intensity of chest pain or any chest pain at rest.
Coronary steal syndrome	Distal to coronary stenosis, vessels are maximally dilated at baseline. Administration of vasodilators (eg, dipyridamole, regadenoson) dilates normal vessels and shunts blood toward well-perfused areas, thereby diverting flow away from vessels that are stenosed and leading to ischemia in myocardium perfused by these vessels. Principle behind pharmacologic stress tests with coronary vasodilators.
Sudden cardiac death	Death from cardiac causes within 1 hour of onset of symptoms, most commonly due to a lethal arrhythmia (eg, VF). Associated with CAD (up to 70% of cases), cardiomyopathy (hypertrophic, dilated), and hereditary ion channelopathies (eg, long QT syndrome, Brugada syndrome). Prevent with implantable cardioverter-defibrillator (ICD).
Chronic ischemic heart disease	Progressive onset of HF over many years due to chronic ischemic myocardial damage.
Myocardial infarction	Most often acute thrombosis due to rupture of coronary artery atherosclerotic plaque. ↑ cardiac biomarkers (CK-MB, troponins) are diagnostic.

ST-segment elevation MI (STEMI)	**Non–ST-segment elevation MI (NSTEMI)**
Transmural infarcts	Subendocardial infarcts
Full thickness of myocardial wall involved	Subendocardium (inner ⅓) especially vulnerable to ischemia
ST elevation on ECG, Q waves	ST depression on ECG

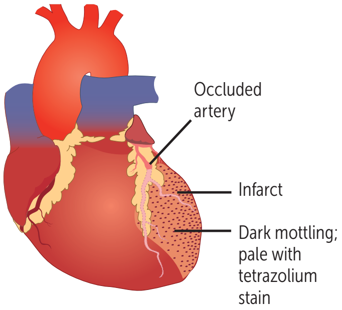
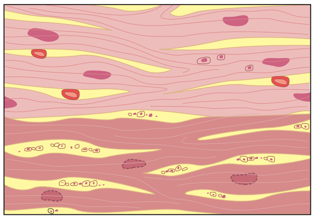
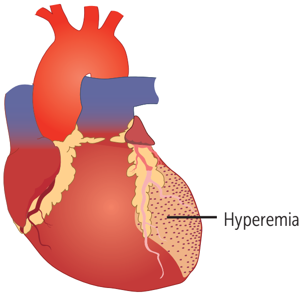
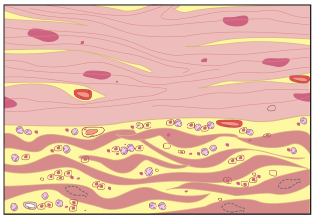
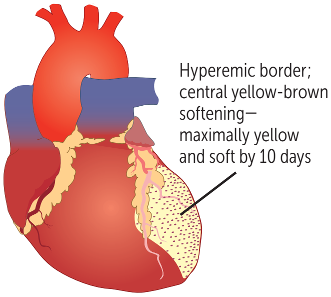
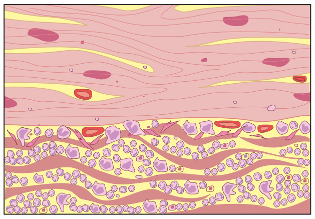
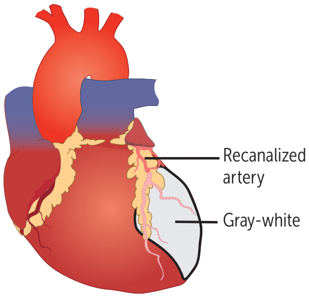
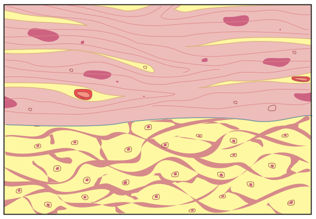




Evolution of myocardial infarction

Commonly occluded coronary arteries: LAD > RCA > circumflex.

Symptoms: diaphoresis, nausea, vomiting, severe retrosternal pain, pain in left arm and/or jaw, shortness of breath, fatigue.

TIME	GROSS	LIGHT MICROSCOPE	COMPLICATIONS
0–24 hr	None  Occluded artery Infarct Dark mottling; pale with tetrazolium stain	Early coagulative necrosis, release of necrotic cell contents into blood; edema, hemorrhage, wavy fibers. Neutrophils appear. Reperfusion injury, associated with generation of free radicals, leads to hypercontraction of myofibrils through ↑ free calcium influx. 	Ventricular arrhythmia, HF, cardiogenic shock.
1–3 days		Extensive coagulative necrosis. Tissue surrounding infarct shows acute inflammation with neutrophils. 	Postinfarction fibrinous pericarditis.
3–14 days	 Hyperemic border; central yellow-brown softening—maximally yellow and soft by 10 days	Macrophages, then granulation tissue at margins. 	Free wall rupture → tamponade; papillary muscle rupture → mitral regurgitation; interventricular septal rupture due to macrophage-mediated structural degradation. LV pseudoaneurysm (risk of rupture).
2 weeks to several months	 Recanalized artery Gray-white	Contracted scar complete. 	Dressler syndrome, HF, arrhythmias, true ventricular aneurysm (risk of mural thrombus).

Diagnosis of myocardial infarction

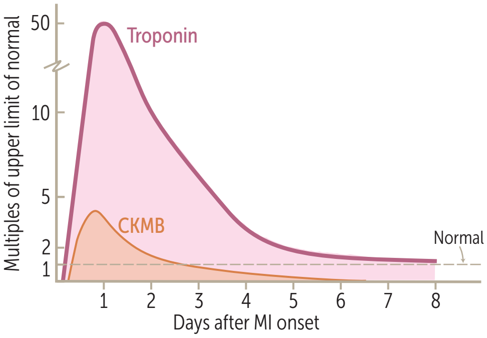
In the first 6 hours, ECG is the gold standard.

Cardiac troponin I rises after 4 hours (peaks at 24 hr) and is ↑ for 7–10 days; more specific than other protein markers.

CK-MB rises after 6–12 hours (peaks at 16–24 hr) and is predominantly found in myocardium but can also be released from skeletal muscle. Useful in diagnosing reinfarction following acute MI because levels return to normal after 48 hours.

Large MIs lead to greater elevations in troponin I and CK-MB. Exact curves vary with testing procedure.

ECG changes can include ST elevation (STEMI, transmural infarct), ST depression (NSTEMI, subendocardial infarct), hyperacute (peaked) T waves, T-wave inversion, new left bundle branch block, and pathologic Q waves or poor R wave progression (evolving or old transmural infarct).

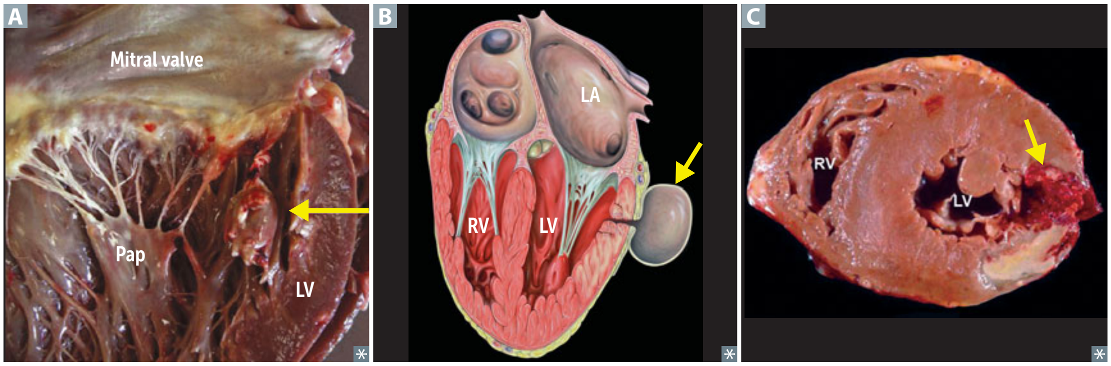


ECG localization of STEMI

INFARCT LOCATION	LEADS WITH ST ELEVATIONS OR Q WAVES
Anteroseptal (LAD)	V_1–V_2
Anteroapical (distal LAD)	V_3–V_4
Anterolateral (LAD or LCX)	V_5–V_6
Lateral (LCX)	I, aV**L**
In**F**erior (RCA)	II, III, aV**F**
Posterior (PDA)	V_7–V_9, ST depression in V_1–V_3 with tall R waves

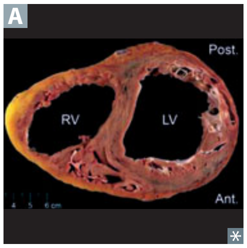
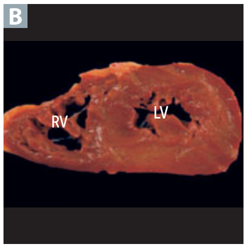
Myocardial infarction complications

Cardiac arrhythmia	Occurs within the first few days after MI. Important cause of death before reaching the hospital and within the first 24 hours post-MI.
Postinfarction fibrinous pericarditis	Occurs 1–3 days after MI. Friction rub.
Papillary muscle rupture	Occurs 2–7 days after MI. Posteromedial papillary muscle rupture A ↑ risk due to single blood supply from posterior descending artery. Can result in severe mitral regurgitation.
Interventricular septal rupture	Occurs 3–5 days after MI. Macrophage-mediated degradation → VSD.
Ventricular pseudoaneurysm formation	Occurs 3–14 days after MI. Contained free wall rupture B; ↓ CO, risk of arrhythmia, embolus from mural thrombus.
Ventricular free wall rupture	Occurs 5–14 days after MI. Free wall rupture C → cardiac tamponade. LV hypertrophy and previous MI protect against free wall rupture.
True ventricular aneurysm	Occurs 2 weeks to several months after MI. Outward bulge with contraction ("dyskinesia"), associated with fibrosis.
Dressler syndrome	Occurs several weeks after MI. Autoimmune phenomenon resulting in fibrinous pericarditis.
LV failure and pulmonary edema	Can occur 2° to LV infarction, VSD, free wall rupture, papillary muscle rupture with mitral regurgitation.

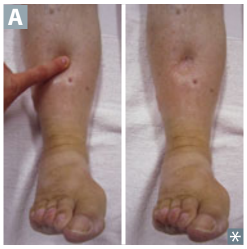


Acute coronary syndrome treatments	**Unstable angina/NSTEMI**—Anticoagulation (eg, heparin), antiplatelet therapy (eg, aspirin) + ADP receptor inhibitors (eg, clopidogrel), β-blockers, ACE inhibitors, statins. Symptom control with nitroglycerin and morphine. **STEMI**—In addition to above, reperfusion therapy most important (percutaneous coronary intervention preferred over fibrinolysis).

Cardiomyopathies

Dilated cardiomyopathy 	Most common cardiomyopathy (90% of cases). Often idiopathic or familial. Other etiologies include chronic Alcohol abuse, wet Beriberi, Coxsackie B viral myocarditis, chronic Cocaine use, Chagas disease, Doxorubicin toxicity, hemochromatosis, sarcoidosis, peripartum cardiomyopathy. Findings: HF, S3, systolic regurgitant murmur, dilated heart on echocardiogram, balloon appearance of heart on CXR. Treatment: Na^+ restriction, ACE inhibitors, β-blockers, diuretics, digoxin, ICD, heart transplant.	Systolic dysfunction ensues. Eccentric hypertrophy A (sarcomeres added in series). ABCCCD. Takotsubo cardiomyopathy: "broken heart syndrome"—ventricular apical ballooning likely due to increased sympathetic stimulation (stressful situations).
Hypertrophic cardiomyopathy 	60–70% of cases are familial, autosomal dominant (most commonly due to mutations in genes encoding sarcomeric proteins, such as myosin binding protein C and β-myosin heavy chain). Can be associated with Friedreich ataxia. Causes syncope during exercise and may lead to sudden death in young athletes due to ventricular arrhythmia. Findings: S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure. Treatment: cessation of high-intensity athletics, use of β-blocker or non-dihydropyridine Ca^{2+} channel blockers (eg, verapamil). ICD if patient is high risk.	Diastolic dysfunction ensues. Marked ventricular concentric hypertrophy (sarcomeres added in parallel) B, often septal predominance. Myofibrillar disarray and fibrosis. Hypertrophic obstructive cardiomyopathy (subset)—asymmetric septal hypertrophy and systolic anterior motion of mitral valve → outflow obstruction → dyspnea, possible syncope.
Restrictive/infiltrative cardiomyopathy	Postradiation fibrosis, Loffler syndrome, Endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Amyloidosis, Sarcoidosis, Hemochromatosis (although dilated cardiomyopathy is more common) (Puppy LEASH).	Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially amyloid). Loffler syndrome—endomyocardial fibrosis with a prominent eosinophilic infiltrate.

Heart failure



Clinical syndrome of cardiac pump dysfunction → congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include S3 heart sound, rales, jugular venous distention (JVD), pitting edema A.

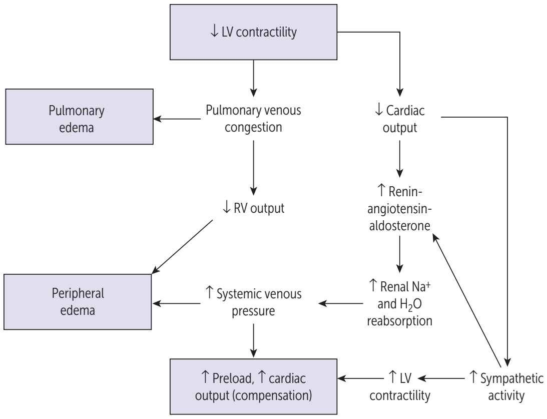
Systolic dysfunction—reduced EF, ↑ EDV; ↓ contractility often 2° to ischemia/MI or dilated cardiomyopathy.

Diastolic dysfunction—preserved EF, normal EDV; ↓ compliance often 2° to myocardial hypertrophy.

Right HF most often results from left HF. Cor pulmonale refers to isolated right HF due to pulmonary cause.

ACE inhibitors or angiotensin II receptor blockers, β-blockers (except in acute decompensated HF), and spironolactone ↓ mortality. Thiazide or loop diuretics are used mainly for symptomatic relief. Hydralazine with nitrate therapy improves both symptoms and mortality in select patients.

Left heart failure	
Orthopnea	Shortness of breath when supine: ↑ venous return from redistribution of blood (immediate gravity effect) exacerbates pulmonary vascular congestion.
Paroxysmal nocturnal dyspnea	Breathless awakening from sleep: ↑ venous return from redistribution of blood, reabsorption of peripheral edema, etc.
Pulmonary edema	↑ pulmonary venous pressure → pulmonary venous distention and transudation of fluid. Presence of hemosiderin-laden macrophages (“HF” cells) in lungs.
Right heart failure	
Hepatomegaly (nutmeg liver)	↑ central venous pressure → ↑ resistance to portal flow. Rarely, leads to “cardiac cirrhosis.”
Jugular venous distention	↑ venous pressure.
Peripheral edema	↑ venous pressure → fluid transudation.


↓ LV contractility
Pulmonary edema
Pulmonary venous congestion
↓ Cardiac output
↓ RV output
↑ Renin-angiotensin-aldosterone
Peripheral edema
↑ Systemic venous pressure
↑ Renal Na⁺ and H₂O reabsorption
↑ Preload, ↑ cardiac output (compensation)
↑ LV contractility
↑ Sympathetic activity

Shock

Inadequate organ perfusion and delivery of nutrients necessary for normal tissue and cellular function. Initially may be reversible but life threatening if not treated promptly.

	CAUSED BY	SKIN	PCWP (PRELOAD)	CO	SVR (AFTERLOAD)	TREATMENT
Hypovolemic	Hemorrhage, dehydration, burns	Cold, clammy	↓↓	↓	↑	IV fluids
Cardiogenic	Acute MI, HF, valvular dysfunction, arrhythmia	Cold, clammy	↑ or ↓	↓↓	↑	Inotropes, diuresis
Obstructive	Cardiac tamponade, pulmonary embolism, tension pneumothorax					Relieve obstruction
Distributive	Sepsis, anaphylaxis CNS injury	Warm Dry	↓ ↓	↑ ↓	↓↓ ↓↓	IV fluids, pressors

Bacterial endocarditis

Fever (most common symptom), new murmur, Roth spots (round white spots on retina surrounded by hemorrhage A), Osler nodes (tender raised lesions on finger or toe pads B due to immune complex deposition), Janeway lesions (small, painless, erythematous lesions on palm or sole) C, glomerulonephritis, septic arterial or pulmonary emboli, splinter hemorrhages D on nail bed. Multiple blood cultures necessary for diagnosis.

- **Acute**—*S aureus* (high virulence). Large vegetations on previously normal valves E. Rapid onset.
- **Subacute**—viridans streptococci (low virulence). Smaller vegetations on congenitally abnormal or diseased valves. Sequela of dental procedures. Gradual onset.

S bovis (gallolyticus) is present in colon cancer, *S epidermidis* on prosthetic valves.

Endocarditis may also be nonbacterial (marantic/thrombotic) 2° to malignancy, hypercoagulable state, or lupus.

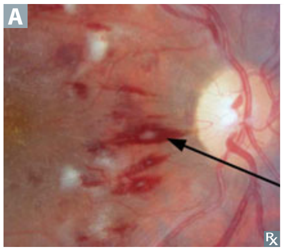
Mitral valve is most frequently involved.

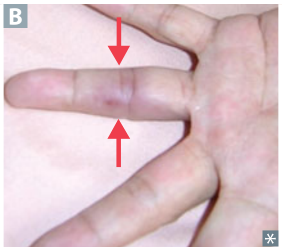
Tricuspid valve endocarditis is associated with IV **drug** abuse (don't "**tri**" **drugs**). Associated with *S aureus*, *Pseudomonas*, and *Candida*.

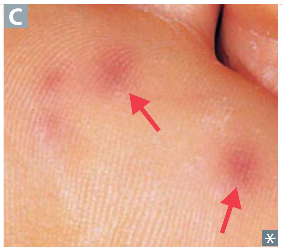
Culture ⊖; most likely *Coxiella burnetii*, *Bartonella* spp., HACEK (*Haemophilus*, *Aggregatibacter* (formerly *Actinobacillus*), *Cardiobacterium*, *Eikenella*, *Kingella)*

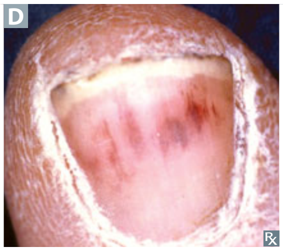
♥ Bacteria **FROM JANE** ♥:

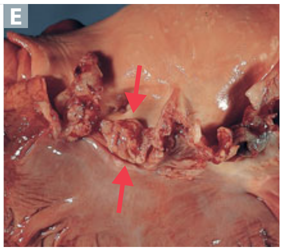
Fever
Roth spots
Osler nodes
Murmur
Janeway lesions
Anemia
Nail-bed hemorrhage
Emboli



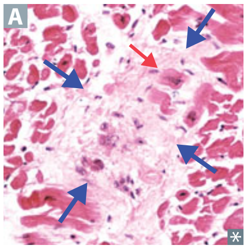








Rheumatic fever



A consequence of pharyngeal infection with group A β-hemolytic streptococci. Late sequelae include rheu**mat**ic heart disease, which affects heart valves—**m**itral > **a**ortic >> **t**ricuspid (high-pressure valves affected most). Early lesion is mitral valve regurgitation; late lesion is mitral stenosis. Associated with Aschoff bodies (granuloma with giant cells [blue arrows in A]), Anitschkow cells (enlarged macrophages with ovoid, wavy, rod-like nucleus [red arrow in A]), ↑ anti-streptolysin O (ASO) titers.

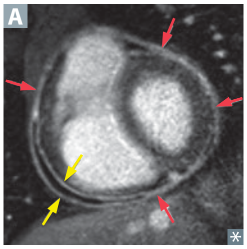
Immune mediated (type II hypersensitivity); not a direct effect of bacteria. Antibodies to M protein cross-react with self antigens (molecular mimicry).

Treatment/prophylaxis: penicillin.

J♥NES (major criteria):

- **J**oint (migratory polyarthritis)
- **♥** (carditis)
- **N**odules in skin (subcutaneous)
- **E**rythema marginatum
- **S**ydenham chorea

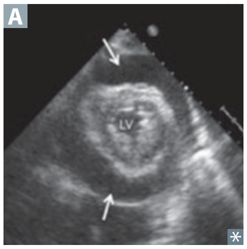
Acute pericarditis



Inflammation of the pericardium [A, red arrows]. Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Often complicated by pericardial effusion [between yellow arrows in A]. Presents with friction rub. ECG changes include widespread ST-segment elevation and/or PR depression.

Causes include idiopathic (most common; presumed viral), confirmed infection (eg, Coxsackievirus), neoplasia, autoimmune (eg, SLE, rheumatoid arthritis), uremia, cardiovascular (acute STEMI or Dressler syndrome), radiation therapy.

Cardiac tamponade



Compression of the heart by fluid (eg, blood, effusions [arrows in A] in pericardial space) → ↓ CO. Equilibration of diastolic pressures in all 4 chambers.

Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), ↑ HR, pulsus paradoxus. ECG shows low-voltage QRS and electrical alternans (due to “swinging” movement of heart in large effusion).

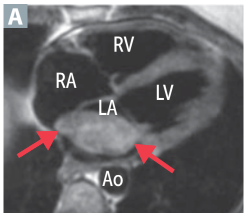
Pulsus paradoxus—↓ in amplitude of systolic BP by > 10 mm Hg during inspiration. Seen in cardiac tamponade, asthma, obstructive sleep apnea, pericarditis, croup.

Syphilitic heart disease

3° syphilis disrupts the vasa vasorum of the aorta with consequent atrophy of vessel wall and dilatation of aorta and valve ring.

May see calcification of aortic root, ascending aortic arch, and thoracic aorta. Leads to “tree bark” appearance of aorta.

Can result in aneurysm of ascending aorta or aortic arch, aortic insufficiency.

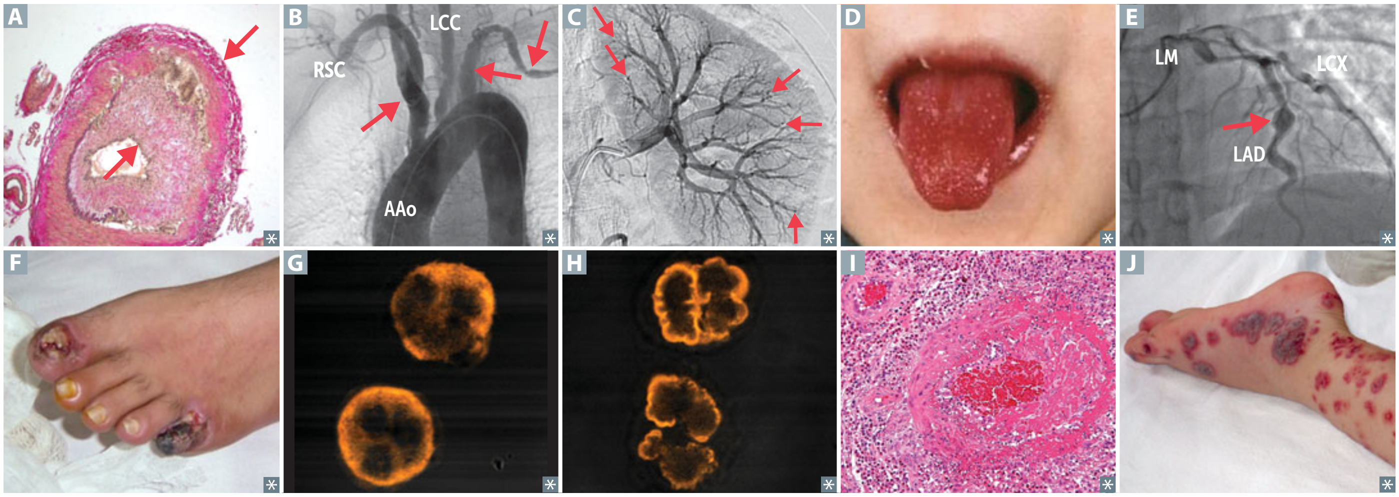
Cardiac tumors	Most common heart tumor is a metastasis (eg, melanoma).
Myxomas 	Most common 1° cardiac tumor (red arrows) in adults A. 90% occur in the atria (mostly left atrium). Myxomas are usually described as a "ball valve" obstruction in the left atrium (associated with multiple syncopal episodes). May auscultate early diastolic "tumor plop" sound. Histology: gelatinous material, myxoma cells immersed in glycosaminoglycans.
Rhabdomyomas	Most frequent 1° cardiac tumor in children (associated with tuberous sclerosis). Histology: hamartomatous growths.
Kussmaul sign	↑ in JVP on inspiration instead of a normal ↓. Inspiration → negative intrathoracic pressure not transmitted to heart → impaired filling of right ventricle → blood backs up into venae cavae → JVD. May be seen with constrictive pericarditis, restrictive cardiomyopathies, right atrial or ventricular tumors.

Vasculitides

	EPIDEMIOLOGY/PRESENTATION	PATHOLOGY/LABS
Large-vessel vasculitis		
Giant cell (temporal) arteritis	Usually elderly females. Unilateral headache (temporal artery), jaw claudication. May lead to irreversible blindness due to ophthalmic artery occlusion. Associated with polymyalgia rheumatica.	Most commonly affects branches of carotid artery. Focal granulomatous inflammation A. ↑ ESR. Treat with high-dose corticosteroids prior to temporal artery biopsy to prevent blindness.
Takayasu arteritis	Usually Asian females < 40 years old. “Pulseless disease” (weak upper extremity pulses), fever, night sweats, arthritis, myalgias, skin nodules, ocular disturbances.	Granulomatous thickening and narrowing of aortic arch and proximal great vessels B. ↑ ESR. Treat with corticosteroids.
Medium-vessel vasculitis		
Polyarteritis nodosa	Usually middle-aged men. Hepatitis B seropositivity in 30% of patients. Fever, weight loss, malaise, headache. GI: abdominal pain, melena. Hypertension, neurologic dysfunction, cutaneous eruptions, renal damage.	Typically involves renal and visceral vessels, not pulmonary arteries. Transmural inflammation of the arterial wall with fibrinoid necrosis. Different stages of inflammation may coexist in different vessels. Innumerable renal microaneurysms C and spasms on arteriogram. Treat with corticosteroids, cyclophosphamide.
Kawasaki disease (mucocutaneous lymph node syndrome)	Asian children < 4 years old. Conjunctival injection, Rash (polymorphous → desquamating), Adenopathy (cervical), Strawberry tongue (oral mucositis) D, Hand-foot changes (edema, erythema), fever.	CRASH and burn. May develop coronary artery aneurysms E; thrombosis or rupture can cause death. Treat with IV immunoglobulin and aspirin.
Buerger disease (thromboangiitis obliterans)	Heavy smokers, males < 40 years old. Intermittent claudication may lead to gangrene F, autoamputation of digits, superficial nodular phlebitis. Raynaud phenomenon is often present.	Segmental thrombosing vasculitis. Treat with smoking cessation.
Small-vessel vasculitis		
Granulomatosis with polyangiitis (Wegener)	Upper respiratory tract: perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis. Lower respiratory tract: hemoptysis, cough, dyspnea. Renal: hematuria, red cell casts.	Triad: ▪ Focal necrotizing vasculitis ▪ Necrotizing granulomas in the lung and upper airway ▪ Necrotizing glomerulonephritis PR3-ANCA/c-ANCA G (anti-proteinase 3). CXR: large nodular densities. Treat with cyclophosphamide, corticosteroids.
Microscopic polyangiitis	Necrotizing vasculitis commonly involving lung, kidneys, and skin with pauci-immune glomerulonephritis and palpable purpura. Presentation similar to granulomatosis with polyangiitis but without nasopharyngeal involvement.	No granulomas. MPO-ANCA/p-ANCA H (anti-myeloperoxidase). Treat with cyclophosphamide, corticosteroids.

Vasculitides *(continued)*

	EPIDEMIOLOGY/PRESENTATION	PATHOLOGY/LABS
Small-vessel vasculitis *(continued)*		
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	Asthma, sinusitis, skin nodules or purpura, peripheral neuropathy (eg, wrist/foot drop). Can also involve heart, GI, kidneys (pauci-immune glomerulonephritis).	Granulomatous, necrotizing vasculitis with eosinophilia I. MPO-ANCA/p-ANCA, ↑ IgE level.
Henoch-Schönlein purpura	Most common childhood systemic vasculitis. Often follows URI. Classic triad: ▪ Skin: palpable purpura on buttocks/legs J ▪ Arthralgias ▪ GI: abdominal pain	Vasculitis 2° to IgA immune complex deposition. Associated with IgA nephropathy (Berger disease).



Hereditary hemorrhagic telangiectasia	Inherited disorder of blood vessels. Findings: blanching skin lesions (telangiectasias), recurrent epistaxis, skin discolorations, arteriovenous malformations (AVMs), GI bleeding, hematuria. Also known as Osler-Weber-Rendu syndrome.

▶ CARDIOVASCULAR—PHARMACOLOGY

Hypertension treatment

Primary (essential) hypertension	Thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers (ARBs), dihydropyridine Ca^{2+} channel blockers.	
Hypertension with heart failure	Diuretics, ACE inhibitors/ARBs, β-blockers (compensated HF), aldosterone antagonists.	β-blockers must be used cautiously in decompensated HF and are contraindicated in cardiogenic shock.
Hypertension with diabetes mellitus	ACE inhibitors/ARBs, Ca^{2+} channel blockers, thiazide diuretics, β-blockers.	ACE inhibitors/ARBs are protective against diabetic nephropathy.
Hypertension in pregnancy	Hydralazine, labetalol, methyldopa, nifedipine.	

Calcium channel blockers

Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (non-dihydropyridines, act on heart).

MECHANISM	Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility. Vascular smooth muscle—amlodipine = nifedipine > diltiazem > verapamil. Heart—verapamil > diltiazem > amlodipine = nifedipine (verapamil = ventricle).
CLINICAL USE	Dihydropyridines (except nimodipine): hypertension, angina (including Prinzmetal), Raynaud phenomenon. Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm). Nicardipine, clevidipine: hypertensive urgency or emergency. Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter.
ADVERSE EFFECTS	Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia, constipation. Dihydropyridine: peripheral edema, flushing, dizziness, gingival hyperplasia.

Hydralazine

MECHANISM	↑ cGMP → smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.
CLINICAL USE	Severe hypertension (particularly acute), HF (with organic nitrate). Safe to use during pregnancy. Frequently coadministered with a β-blocker to prevent reflex tachycardia.
ADVERSE EFFECTS	Compensatory tachycardia (contraindicated in angina/CAD), fluid retention, headache, angina. Lupus-like syndrome.

Hypertensive emergency

Treat with clevidipine, fenoldopam, labetalol, nicardipine, or nitroprusside.

Nitroprusside	Short acting; ↑ cGMP via direct release of NO. Can cause cyanide toxicity (releases cyanide).
Fenoldopam	Dopamine D$_1$ receptor agonist—coronary, peripheral, renal, and splanchnic vasodilation. ↓ BP, ↑ natriuresis. Also used postoperatively as an antihypertensive. Can cause hypotension and tachycardia.

Nitrates	Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate.
MECHANISM	Vasodilate by ↑ NO in vascular smooth muscle → ↑ in cGMP and smooth muscle relaxation. Dilate veins >> arteries. ↓ preload.
CLINICAL USE	Angina, acute coronary syndrome, pulmonary edema.
ADVERSE EFFECTS	Reflex tachycardia (treat with β-blockers), hypotension, flushing, headache, "Monday disease" in industrial exposure: development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend → tachycardia, dizziness, headache upon reexposure. Contraindicated in right ventricular infarction.

Antianginal therapy

Goal is reduction of myocardial O_2 consumption (MVO_2) by ↓ 1 or more of the determinants of MVO_2: end-diastolic volume, BP, HR, contractility.

COMPONENT	NITRATES	β-BLOCKERS	NITRATES + β-BLOCKERS
End-diastolic volume	↓	No effect or ↑	No effect or ↓
Blood pressure	↓	↓	↓
Contractility	No effect	↓	Little/no effect
Heart rate	↑ (reflex response)	↓	No effect or ↓
Ejection time	↓	↑	Little/no effect
MVO_2	↓	↓	↓↓

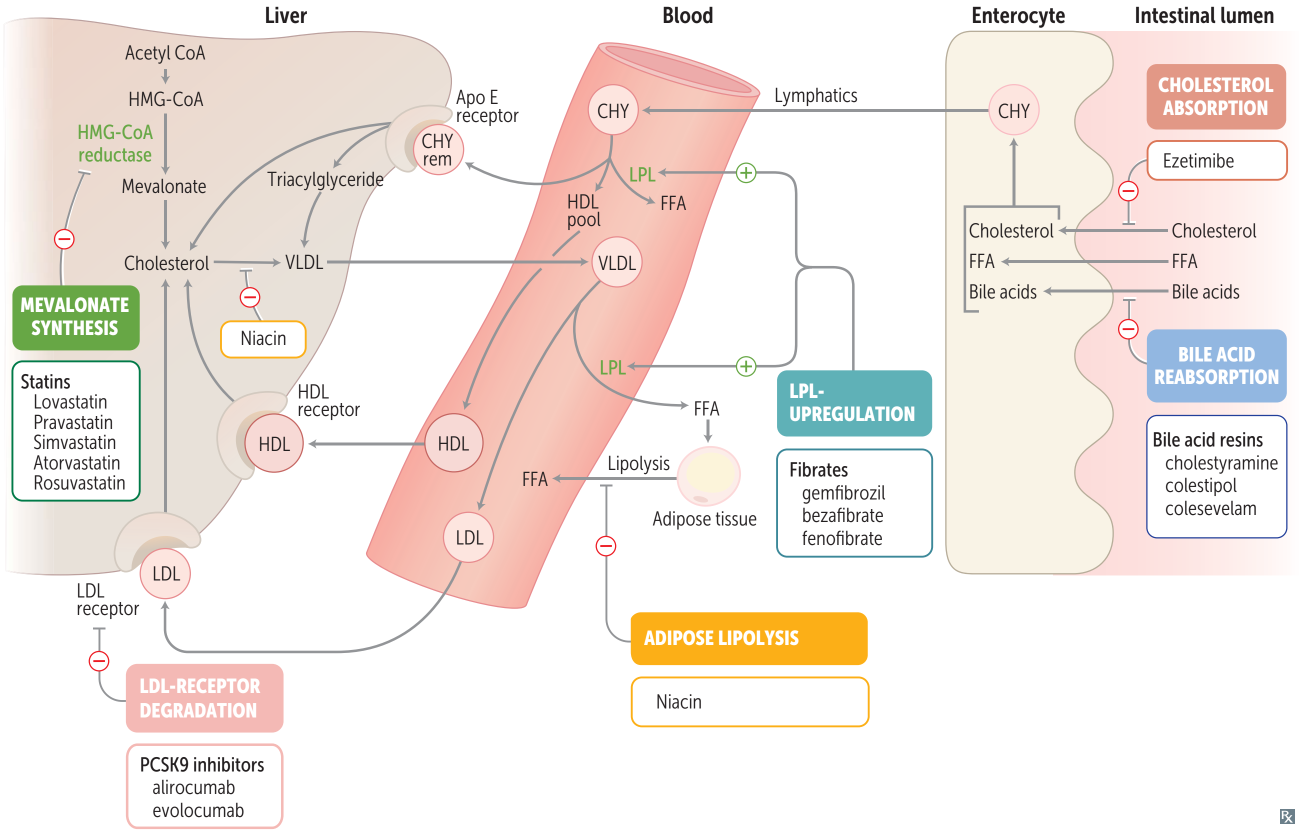
Verapamil is similar to β-blockers in effect.
Pindolol and acebutolol are partial β-agonists that should be used with caution in angina.

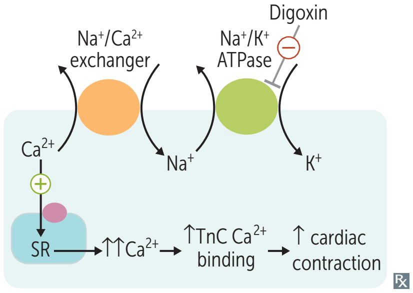
Ranolazine	
MECHANISM	Inhibits the late phase of sodium current thereby reducing diastolic wall tension and oxygen consumption. Does not affect heart rate or contractility.
CLINICAL USE	Angina refractory to other medical therapies.
ADVERSE EFFECTS	Constipation, dizziness, headache, nausea, QT prolongation.

Milrinone	
MECHANISM	Selective PDE-3 inhibitor. In cardiomyocytes: ↑ cAMP accumulation → ↑ Ca^{2+} influx → ↑ inotropy and chronotropy. In vascular smooth muscle: ↑ cAMP accumulation → inhibition of MLCK activity → general vasodilation.
CLINICAL USE	Short-term use in acute decompensated HF.
ADVERSE EFFECTS	Arrhythmias, hypotension.

Lipid-lowering agents

DRUG	LDL	HDL	TRIGLYCERIDES	MECHANISMS OF ACTION	ADVERSE EFFECTS/PROBLEMS
HMG-CoA reductase inhibitors (eg, lovastatin, pravastatin)	↓↓↓	↑	↓	Inhibit conversion of HMG-CoA to mevalonate, a cholesterol precursor; ↓ mortality in CAD patients	Hepatotoxicity (↑ LFTs), myopathy (esp. when used with fibrates or niacin)
Bile acid resins Cholestyramine, colestipol, colesevelam	↓↓	Slightly ↑	Slightly ↑	Prevent intestinal reabsorption of bile acids; liver must use cholesterol to make more	GI upset, ↓ absorption of other drugs and fat-soluble vitamins
Ezetimibe	↓↓	↑/—	↓/—	Prevent cholesterol absorption at small intestine brush border	Rare ↑ LFTs, diarrhea
Fibrates Gemfibrozil, bezafibrate, fenofibrate	↓	↑	↓↓↓	Upregulate LPL → ↑ TG clearance Activates PPAR-α to induce HDL synthesis	Myopathy (↑ risk with statins), cholesterol gallstones
Niacin (vitamin B_3)	↓↓	↑↑	↓	Inhibits lipolysis (hormone-sensitive lipase) in adipose tissue; reduces hepatic VLDL synthesis	Red, flushed face, which is ↓ by NSAIDs or long-term use Hyperglycemia Hyperuricemia
PCSK9 inhibitors Alirocumab, evolocumab	↓↓↓	↑	↓	Inactivation of LDL-receptor degradation, increasing amount of LDL removed from bloodstream	Myalgias, delirium, dementia, other neurocognitive effects


Liver
Blood
Enterocyte
Intestinal lumen
Acetyl CoA
HMG-CoA
HMG-CoA reductase
Mevalonate
Cholesterol
VLDL
Triacylglyceride
Apo E receptor
CHY rem
MEVALONATE SYNTHESIS
Statins
Lovastatin
Pravastatin
Simvastatin
Atorvastatin
Rosuvastatin
Niacin
HDL receptor
HDL
LDL
LDL receptor
LDL-RECEPTOR DEGRADATION
PCSK9 inhibitors
alirocumab
evolocumab
CHY
Lymphatics
LPL
FFA
HDL pool
VLDL
LPL
FFA
HDL
Lipolysis
FFA
Adipose tissue
LDL
ADIPOSE LIPOLYSIS
Niacin
LPL-UPREGULATION
Fibrates
gemfibrozil
bezafibrate
fenofibrate
CHY
Cholesterol
FFA
Bile acids
CHOLESTEROL ABSORPTION
Ezetimibe
Cholesterol
FFA
Bile acids
BILE ACID REABSORPTION
Bile acid resins
cholestyramine
colestipol
colesevelam

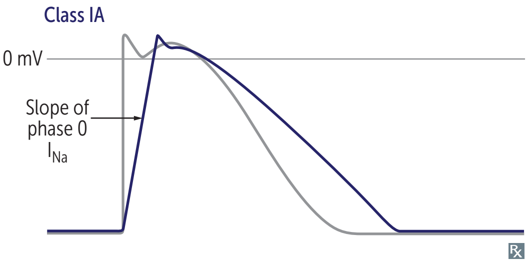
Cardiac glycosides	Digoxin.
MECHANISM	Direct inhibition of Na^+/K^+ ATPase → indirect inhibition of Na^+/Ca^{2+} exchanger. ↑ $[Ca^{2+}]_i$ → positive inotropy. Stimulates vagus nerve → ↓ HR.  Digoxin Na+/Ca2+ exchanger Na+/K+ ATPase Ca2+ Na+ K+ SR ↑↑Ca2+ ↑TnC Ca2+ binding ↑ cardiac contraction
CLINICAL USE	HF (↑ contractility); atrial fibrillation (↓ conduction at AV node and depression of SA node).
ADVERSE EFFECTS	Cholinergic—nausea, vomiting, diarrhea, blurry yellow vision (think van Gogh), arrhythmias, AV block. Can lead to hyperkalemia, which indicates poor prognosis. Factors predisposing to toxicity: renal failure (↓ excretion), hypokalemia (permissive for digoxin binding at K^+-binding site on Na^+/K^+ ATPase), drugs that displace digoxin from tissue-binding sites, and ↓ clearance (eg, verapamil, amiodarone, quinidine).
ANTIDOTE	Slowly normalize K^+, cardiac pacer, anti-digoxin Fab fragments, Mg^{2+}.

Antiarrhythmics—sodium channel blockers (class I)

Slow or block (↓) conduction (especially in depolarized cells). ↓ slope of phase 0 depolarization. Are state dependent (selectively depress tissue that is frequently depolarized [eg, tachycardia]).

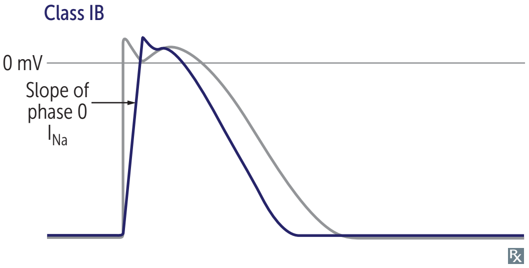
Class IA

	Quinidine, **P**rocainamide, **D**iso**pyramid**e. "The **Q**ueen **P**roclaims **D**iso's **pyramid**."
MECHANISM	↑ AP duration, ↑ effective refractory period (ERP) in ventricular action potential, ↑ QT interval, some potassium channel blocking effects.
CLINICAL USE	Both atrial and ventricular arrhythmias, especially re-entrant and ectopic SVT and VT.
ADVERSE EFFECTS	Cinchonism (headache, tinnitus with quinidine), reversible SLE-like syndrome (procainamide), HF (disopyramide), thrombocytopenia, torsades de pointes due to ↑ QT interval.



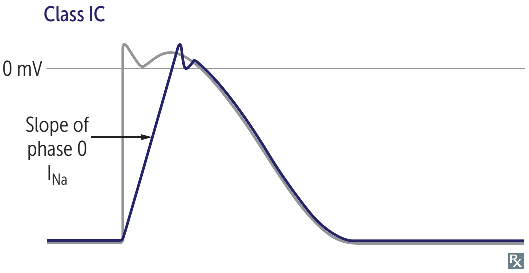
Class **IB**

	Lidocaine, **Mexi**le**T**ine. "**I**'d **B**uy **Lidd**y's **Mexi**can **T**acos."
MECHANISM	↓ AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue. Phenytoin can also fall into the IB category.
CLINICAL USE	Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias. **IB** is **B**est post-MI.
ADVERSE EFFECTS	CNS stimulation/depression, cardiovascular depression.

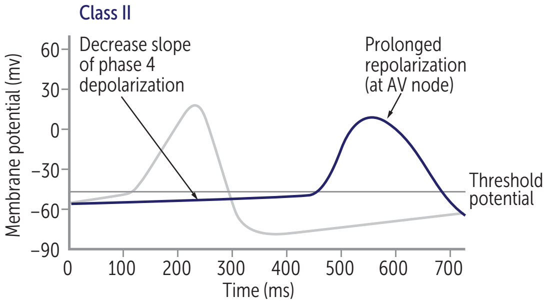


Class **IC**

	Flecainide, **P**ropafenone. "**C**an I have **F**ries, **P**lease."
MECHANISM	Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue. Minimal effect on AP duration.
CLINICAL USE	SVTs, including atrial fibrillation. Only as a last resort in refractory VT.
ADVERSE EFFECTS	Proarrhythmic, especially post-MI (contraindicated). **IC** is **C**ontraindicated in structural and ischemic heart disease.

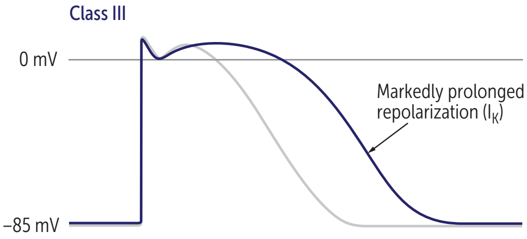


Antiarrhythmics—β-blockers (class II)	Metoprolol, propranolol, esmolol, atenolol, timolol, carvedilol.
MECHANISM	Decrease SA and AV nodal activity by ↓ cAMP, ↓ Ca^{2+} currents. Suppress abnormal pacemakers by ↓ slope of phase 4. AV node particularly sensitive—↑ PR interval. Esmolol very short acting.
CLINICAL USE	SVT, ventricular rate control for atrial fibrillation and atrial flutter.
ADVERSE EFFECTS	Impotence, exacerbation of COPD and asthma, cardiovascular effects (bradycardia, AV block, HF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia. Metoprolol can cause dyslipidemia. Propranolol can exacerbate vasospasm in Prinzmetal angina. β-blockers (except the nonselective α- and β-antagonists carvedilol and labetalol) cause unopposed α_1-agonism if given alone for pheochromocytoma or cocaine toxicity. Treat β-blocker overdose with saline, atropine, glucagon.



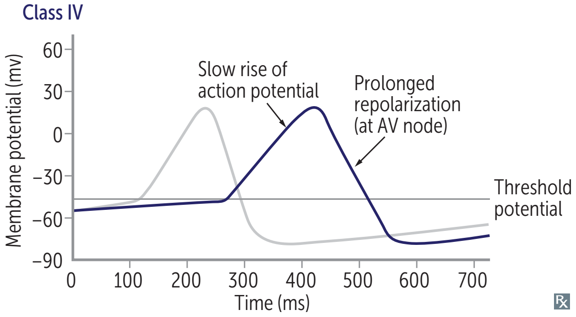
Pacemaker cell action potential

Antiarrhythmics—potassium channel blockers (class III)	Amiodarone, Ibutilide, Dofetilide, Sotalol.	AIDS.
MECHANISM	↑ AP duration, ↑ ERP, ↑ QT interval.	
CLINICAL USE	Atrial fibrillation, atrial flutter; ventricular tachycardia (amiodarone, sotalol).	
ADVERSE EFFECTS	Sotalol—torsades de pointes, excessive β blockade. Ibutilide—torsades de pointes. Amiodarone—pulmonary fibrosis, hepatotoxicity, hypothyroidism/hyperthyroidism (amiodarone is 40% iodine by weight), acts as hapten (corneal deposits, blue/gray skin deposits resulting in photodermatitis), neurologic effects, constipation, cardiovascular effects (bradycardia, heart block, HF).	Remember to check PFTs, LFTs, and TFTs when using amiodarone. Amiodarone is lipophilic and has class I, II, III, and IV effects.



Cell action potential

Antiarrhythmics—calcium channel blockers (class IV)	Verapamil, diltiazem.
MECHANISM	↓ conduction velocity, ↑ ERP, ↑ PR interval.
CLINICAL USE	Prevention of nodal arrhythmias (eg, SVT), rate control in atrial fibrillation.
ADVERSE EFFECTS	Constipation, flushing, edema, cardiovascular effects (HF, AV block, sinus node depression).



Other antiarrhythmics

Adenosine	↑ K^+ out of cells → hyperpolarizing the cell and ↓ I_{Ca}, decreasing AV node conduction. Drug of choice in diagnosing/terminating certain forms of SVT. Very short acting (~ 15 sec). Effects blunted by theophylline and caffeine (both are adenosine receptor antagonists). Adverse effects include flushing, hypotension, chest pain, sense of impending doom, bronchospasm.
Mg^{2+}	Effective in torsades de pointes and digoxin toxicity.

Ivabradine

MECHANISM	Selective inhibition of funny sodium channels (I_f), prolonging slow depolarization phase (phase 4). ↓ SA node firing; negative chronotropic effect without inotropy. Reduces cardiac O_2 requirement.
CLINICAL USE	Chronic stable angina in patients who cannot take β-blockers. Chronic HF with reduced ejection fraction.
ADVERSE EFFECTS	Luminous phenomena/visual brightness, hypertension, bradycardia.

Endocrine

"If you skew the endocrine system, you lose the pathways to self."

—Hilary Mantel

"We have learned that there is an endocrinology of elation and despair, a chemistry of mystical insight, and, in relation to the autonomic nervous system, a meteorology and even . . . an astro-physics of changing moods."

—Aldous (Leonard) Huxley

"Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy."

—Elaine Sherman, *Book of Divine Indulgences*

▸ Embryology 312

▸ Anatomy 312

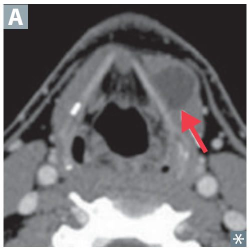
▸ Physiology 314

▸ Pathology 323

▸ Pharmacology 340

▶ ENDOCRINE—EMBRYOLOGY

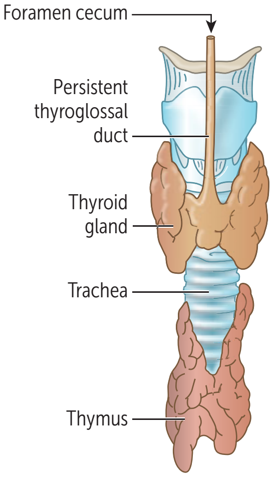
Thyroid development



Thyroid diverticulum arises from floor of primitive pharynx and descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as cysts or the pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct. Most common ectopic thyroid tissue site is the tongue (lingual thyroid). Removal may result in hypothyroidism if it is the only thyroid tissue present.

Thyroglossal duct cyst A presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue (vs persistent cervical sinus leading to branchial cleft cyst in lateral neck).

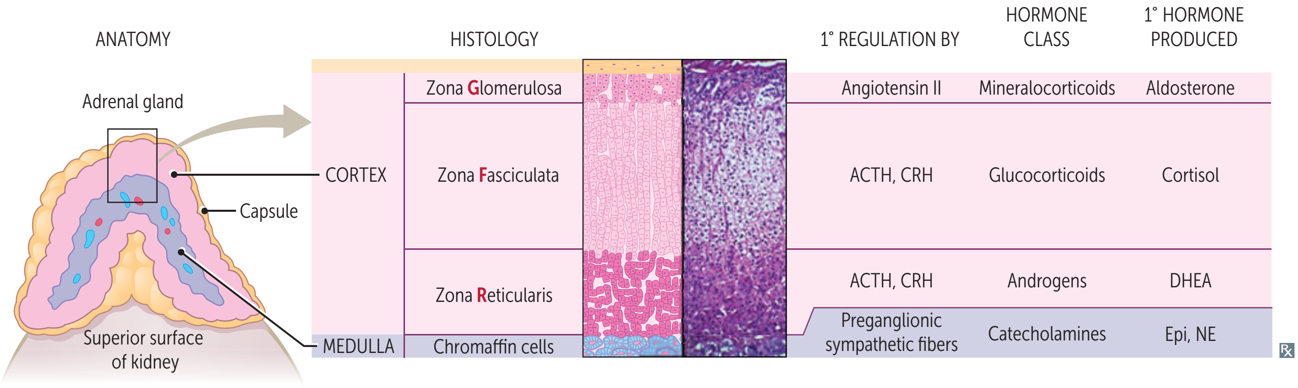
Thyroid tissue and parafollicular cells (aka, C cells, produce Calcitonin) of the thyroid are derived from endoderm.



▶ ENDOCRINE—ANATOMY

Adrenal cortex and medulla

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).

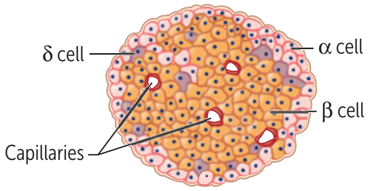


	HISTOLOGY	1° REGULATION BY	HORMONE CLASS	1° HORMONE PRODUCED
CORTEX	Zona **G**lomerulosa	Angiotensin II	Mineralocorticoids	Aldosterone
	Zona **F**asciculata	ACTH, CRH	Glucocorticoids	Cortisol
	Zona **R**eticularis	ACTH, CRH	Androgens	DHEA
MEDULLA	Chromaffin cells	Preganglionic sympathetic fibers	Catecholamines	Epi, NE

GFR corresponds with Salt (mineralocorticoids), Sugar (glucocorticoids), and Sex (androgens). "The deeper you go, the sweeter it gets."

Pituitary gland

Anterior pituitary (adenohypophysis)	Secretes FSH, LH, ACTH, TSH, prolactin, GH. Melanotropin (MSH) secreted from intermediate lobe of pituitary. Derived from oral ectoderm (Rathke pouch). ▪ α subunit—hormone subunit common to TSH, LH, FSH, and hCG. ▪ β subunit—determines hormone specificity.	ACTH and MSH are derivatives of proopiomelanocortin (POMC). FLAT PiG: FSH, LH, ACTH, TSH, PRL, GH. B-FLAT: Basophils—FSH, LH, ACTH, TSH. Acidophils: GH, PRL.
Posterior pituitary (neurohypophysis)	Stores and releases vasopressin (antidiuretic hormone, or ADH) and oxytocin, both made in the hypothalamus (supraoptic and paraventricular nuclei) and transported to posterior pituitary via neurophysins (carrier proteins). Derived from neuroectoderm.	

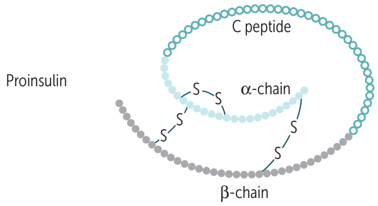
Endocrine pancreas cell types	Islets of Langerhans are collections of α, β, and δ endocrine cells. Islets arise from pancreatic buds. ▪ α = glucagon (peripheral) ▪ β = insulin (central) ▪ δ = somatostatin (interspersed)	Insulin (β cells) inside. 

▸ ENDOCRINE—PHYSIOLOGY

Insulin

SYNTHESIS

Preproinsulin (synthesized in RER) → cleavage of "presignal" → proinsulin (stored in secretory granules) → cleavage of proinsulin → exocytosis of insulin and C-peptide equally. Insulin and C-peptide are ↑ in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.


Proinsulin
C peptide
S
S
α-chain
S
S
S
S
β-chain

SOURCE

Released from pancreatic β cells.

FUNCTION

Binds insulin receptors (tyrosine kinase activity ①), inducing glucose uptake (carrier-mediated transport) into insulin-dependent tissue ② and gene transcription.

Anabolic effects of insulin:

- ↑ glucose transport in skeletal muscle and adipose tissue
- ↑ glycogen synthesis and storage
- ↑ triglyceride synthesis
- ↑ Na$^+$ retention (kidneys)
- ↑ protein synthesis (muscles)
- ↑ cellular uptake of K$^+$ and amino acids
- ↓ glucagon release
- ↓ lipolysis in adipose tissue

Unlike glucose, insulin does not cross placenta.

Insulin-dependent glucose transporters:

- GLUT4: adipose tissue, striated muscle (exercise can also increase GLUT4 expression)

Insulin-independent transporters:

- GLUT1: RBCs, brain, cornea, placenta
- GLUT2 (bidirectional): β islet cells, liver, kidney, small intestine
- GLUT3: brain, placenta
- GLUT5 (fructose): spermatocytes, GI tract

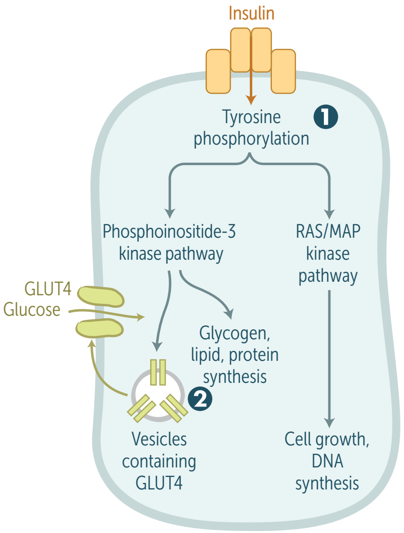
Brain utilizes glucose for metabolism normally and ketone bodies during starvation. RBCs utilize glucose because they lack mitochondria for aerobic metabolism.

BRICK L (insulin-independent glucose uptake): **B**rain, **R**BCs, **I**ntestine, **C**ornea, **K**idney, **L**iver.

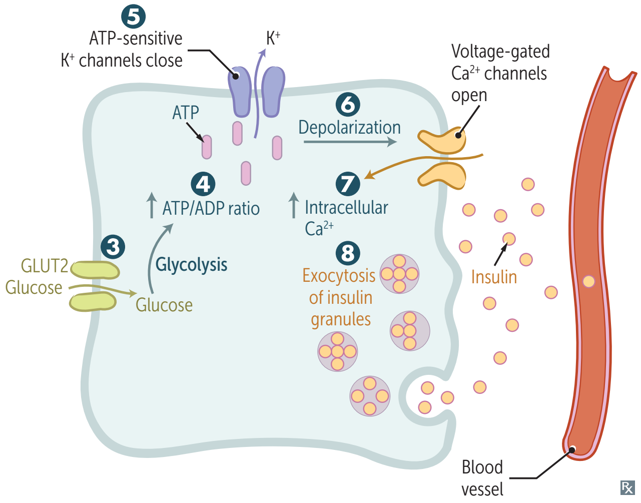
REGULATION

Glucose is the major regulator of insulin release. ↑ insulin response with oral vs IV glucose because of incretins such as glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are released after meals and ↑ β cell sensitivity to glucose. Release ↓ by α$_2$, ↑ by β$_2$ (2 = regulates insulin)

Glucose enters β cells ③ → ↑ ATP generated from glucose metabolism ④ closes K$^+$ channels (target of sulfonylureas) ⑤ and depolarizes β cell membrane ⑥. Voltage-gated Ca^{2+} channels open → Ca^{2+} influx ⑦ and stimulation of insulin exocytosis ⑧.


Insulin
Tyrosine phosphorylation
①
Phosphoinositide-3 kinase pathway
RAS/MAP kinase pathway
GLUT4
Glucose
Glycogen, lipid, protein synthesis
②
Vesicles containing GLUT4
Cell growth, DNA synthesis

Insulin-dependent glucose uptake


⑤
ATP-sensitive K+ channels close
K+
Voltage-gated Ca2+ channels open
ATP
⑥
Depolarization
④
↑ ATP/ADP ratio
⑦
↑ Intracellular Ca2+
③
GLUT2
Glucose
Glycolysis
Glucose
⑧
Exocytosis of insulin granules
Insulin
Blood vessel

Insulin secretion by pancreatic β cells

Glucagon

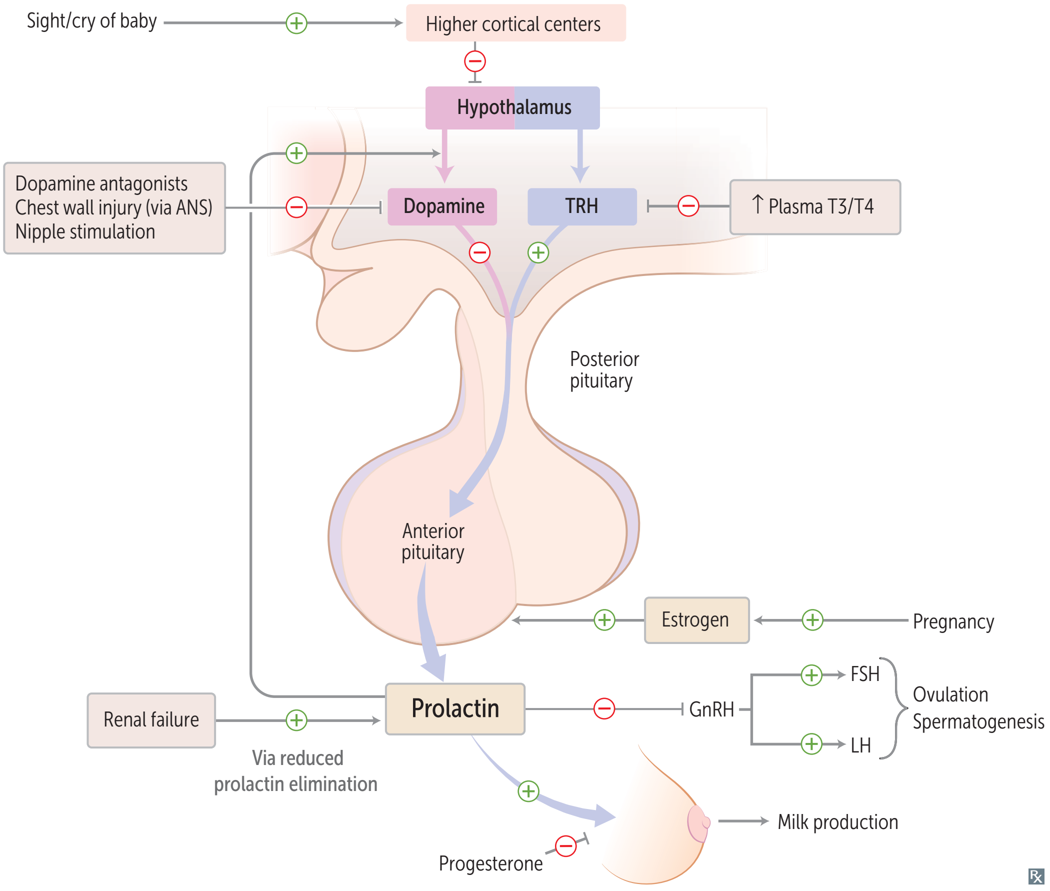
SOURCE	Made by α cells of pancreas.
FUNCTION	Glycogenolysis, gluconeogenesis, lipolysis, ketone production.
REGULATION	Secreted in response to hypoglycemia. Inhibited by insulin, hyperglycemia, and somatostatin.

Hypothalamic-pituitary hormones

HORMONE	FUNCTION	CLINICAL NOTES
CRH	↑ ACTH, MSH, β-endorphin	↓ in chronic exogenous steroid use.
Dopamine	↓ prolactin, TSH	Dopamine antagonists (eg, antipsychotics) can cause galactorrhea due to hyperprolactinemia.
GHRH	↑ GH	Analog (tesamorelin) used to treat HIV-associated lipodystrophy.
GnRH	↑ FSH, LH	Suppressed by hyperprolactinemia. Tonic GnRH suppresses HPG axis. Pulsatile GnRH leads to puberty, fertility.
Prolactin	↓ GnRH	Pituitary prolactinoma → amenorrhea, osteoporosis, hypogonadism, galactorrhea.
Somatostatin	↓ GH, TSH	Analogs used to treat acromegaly.
TRH	↑ TSH, prolactin	↑ TRH (eg, in 1°/2° hypothyroidism) may increase prolactin secretion → galactorrhea.

Prolactin

SOURCE	Secreted mainly by anterior pituitary.	Structurally homologous to growth hormone.
FUNCTION	Stimulates milk production in breast; inhibits ovulation in females and spermatogenesis in males by inhibiting GnRH synthesis and release.	Excessive amounts of prolactin associated with ↓ libido.
REGULATION	Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from tuberoinfundibular pathway of hypothalamus. Prolactin in turn inhibits its own secretion by ↑ dopamine synthesis and secretion from hypothalamus. TRH ↑ prolactin secretion (eg, in 1° or 2° hypothyroidism).	Dopamine agonists (eg, bromocriptine) inhibit prolactin secretion and can be used in treatment of prolactinoma. Dopamine antagonists (eg, most antipsychotics) and estrogens (eg, OCPs, pregnancy) stimulate prolactin secretion.


Sight/cry of baby
Higher cortical centers
Hypothalamus
Dopamine antagonists
Chest wall injury (via ANS)
Nipple stimulation
Dopamine
TRH
↑ Plasma T3/T4
Posterior pituitary
Anterior pituitary
Estrogen
Pregnancy
Renal failure
Prolactin
GnRH
FSH
LH
Ovulation
Spermatogenesis
Via reduced prolactin elimination
Milk production
Progesterone

Growth hormone (somatotropin)

SOURCE	Secreted by anterior pituitary.	
FUNCTION	Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. ↑ insulin resistance (diabetogenic).	Somato**stat**in keeps your growth **stat**ic. Somato**medi**n **medi**ates your growth.
REGULATION	Released in pulses in response to growth hormone–releasing hormone (GHRH). Secretion ↑ during exercise, deep sleep, puberty, hypoglycemia. Secretion inhibited by glucose and somatostatin release via negative feedback by somatomedin.	Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treat with somatostatin analogs (eg, octreotide) or surgery.

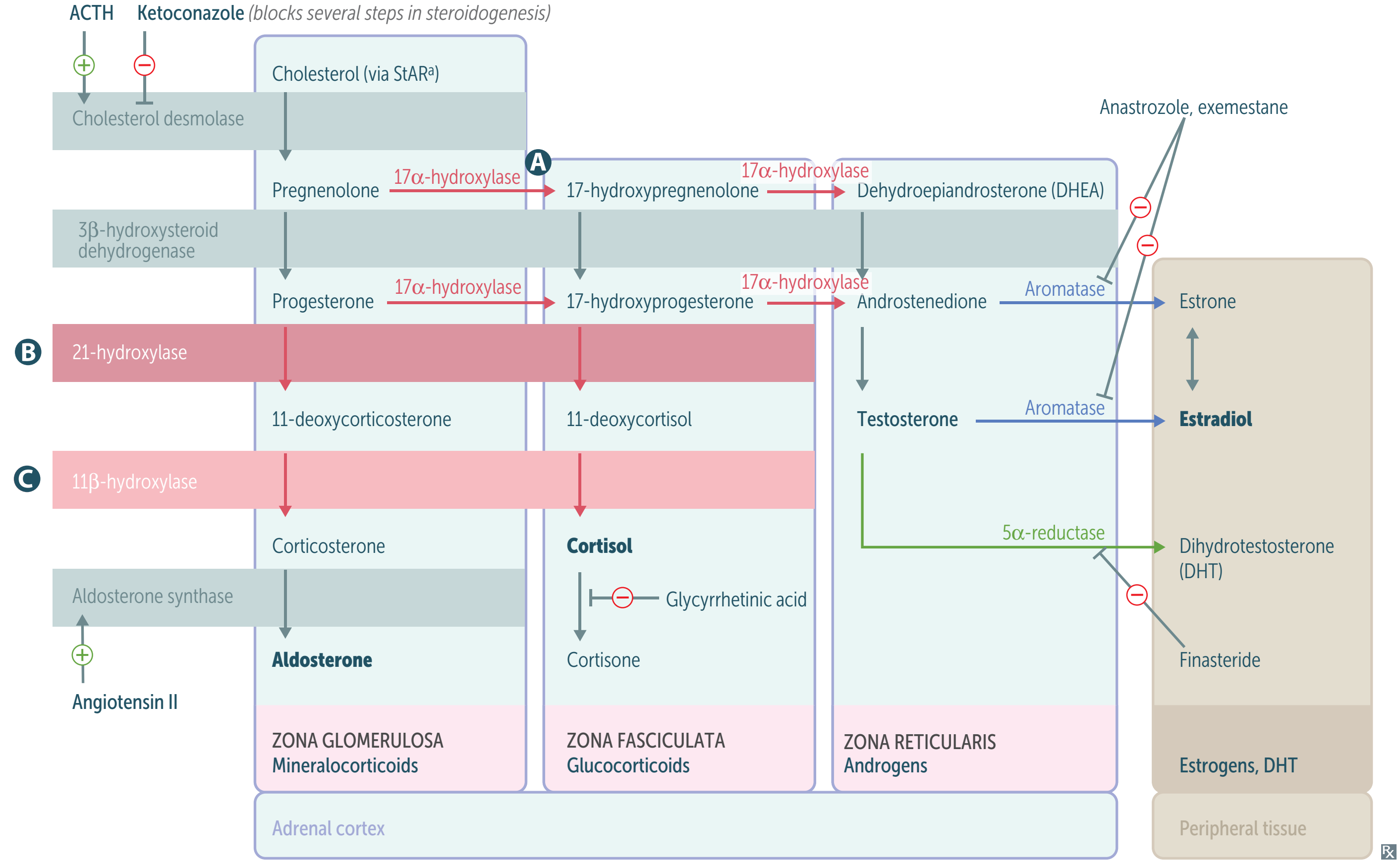
Appetite regulation

Ghrelin	Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor). Produced by stomach. Sleep deprivation or Prader-Willi syndrome → ↑ ghrelin production.	**Ghre**lin makes you hun**ghre**.
Leptin	Satiety hormone. Produced by adipose tissue. Mutation of leptin gene → congenital obesity. Sleep deprivation or starvation → ↓ leptin production.	Lept**in** keeps you th**in**.
Endocannabinoids	Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite.	Exogenous cannabinoids cause "the munchies."

Antidiuretic hormone

SOURCE	Synthesized in hypothalamus (supraoptic nuclei), stored and secreted by posterior pituitary.	
FUNCTION	Regulates serum osmolarity (V_2-receptors) and blood pressure (V_1-receptors). Primary function is serum osmolarity regulation (ADH ↓ serum osmolarity, ↑ urine osmolarity) via regulation of aquaporin channel insertion in principal cells of renal collecting duct.	ADH level is ↓ in central diabetes insipidus (DI), normal or ↑ in nephrogenic DI. Nephrogenic DI can be caused by mutation in V_2-receptor. Desmopressin acetate (ADH analog) is a treatment for central DI and nocturnal enuresis.
REGULATION	Osmoreceptors in hypothalamus (1°); hypovolemia.	

Adrenal steroids and congenital adrenal hyperplasias


ACTH
Ketoconazole (blocks several steps in steroidogenesis)
Cholesterol (via StAR[a])
Cholesterol desmolase
Pregnenolone
17α-hydroxylase
A
17-hydroxypregnenolone
17α-hydroxylase
Dehydroepiandrosterone (DHEA)
Anastrozole, exemestane
3β-hydroxysteroid dehydrogenase
Progesterone
17α-hydroxylase
17-hydroxyprogesterone
17α-hydroxylase
Androstenedione
Aromatase
Estrone
B
21-hydroxylase
11-deoxycorticosterone
11-deoxycortisol
Testosterone
Aromatase
Estradiol
C
11β-hydroxylase
Corticosterone
Cortisol
5α-reductase
Dihydrotestosterone (DHT)
Aldosterone synthase
Glycyrrhetinic acid
Aldosterone
Cortisone
Finasteride
Angiotensin II
ZONA GLOMERULOSA
Mineralocorticoids
ZONA FASCICULATA
Glucocorticoids
ZONA RETICULARIS
Androgens
Estrogens, DHT
Adrenal cortex
Peripheral tissue

[a] Rate-limiting step.

ENZYME DEFICIENCY	MINERALOCORTICOIDS	CORTISOL	SEX HORMONES	BP	[K+]	LABS	PRESENTATION
A 17α-hydroxylase[a]	↑	↓	↓	↑	↓	↓ androstenedione	XY: ambiguous genitalia, undescended testes XX: lacks 2° sexual development
B 21-hydroxylase[a]	↓	↓	↑	↓	↑	↑ renin activity ↑ 17-hydroxyprogesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
C 11β-hydroxylase[a]	↓ aldosterone ↑ 11-deoxycorticosterone (results in ↑ BP)	↓	↑	↑	↓	↓ renin activity	XX: virilization

[a] All congenital adrenal enzyme deficiencies are characterized by an enlargement of both adrenal glands due to ↑ ACTH stimulation (in response to ↓ cortisol) and by skin hyperpigmentation.

Cortisol

SOURCE	Adrenal zona fasciculata.	Bound to corticosteroid-binding globulin.
FUNCTION	↑ **A**ppetite ↑ **B**lood pressure: - Upregulates α_1-receptors on arterioles → ↑ sensitivity to norepinephrine and epinephrine (permissive action) - At high concentrations, can bind to mineralocorticoid (aldosterone) receptors ↑ **I**nsulin resistance (diabetogenic) ↑ **G**luconeogenesis, lipolysis, and proteolysis (↓ glucose utilization) ↓ **F**ibroblast activity (poor wound healing, ↓ collagen synthesis, ↑ striae) ↓ **I**nflammatory and **I**mmune responses: - Inhibits production of leukotrienes and prostaglandins - Inhibits WBC adhesion → neutrophilia - Blocks histamine release from mast cells - Eosinopenia, lymphopenia - Blocks IL-2 production ↓ **B**one formation (↓ osteoblast activity)	Cortisol is a **A BIG FIB**. Exogenous corticosteroids can cause reactivation of TB and candidiasis (blocks IL-2 production).
REGULATION	CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata. Excess cortisol ↓ CRH, ACTH, and cortisol secretion.	Chronic stress induces prolonged secretion.

Calcium homeostasis

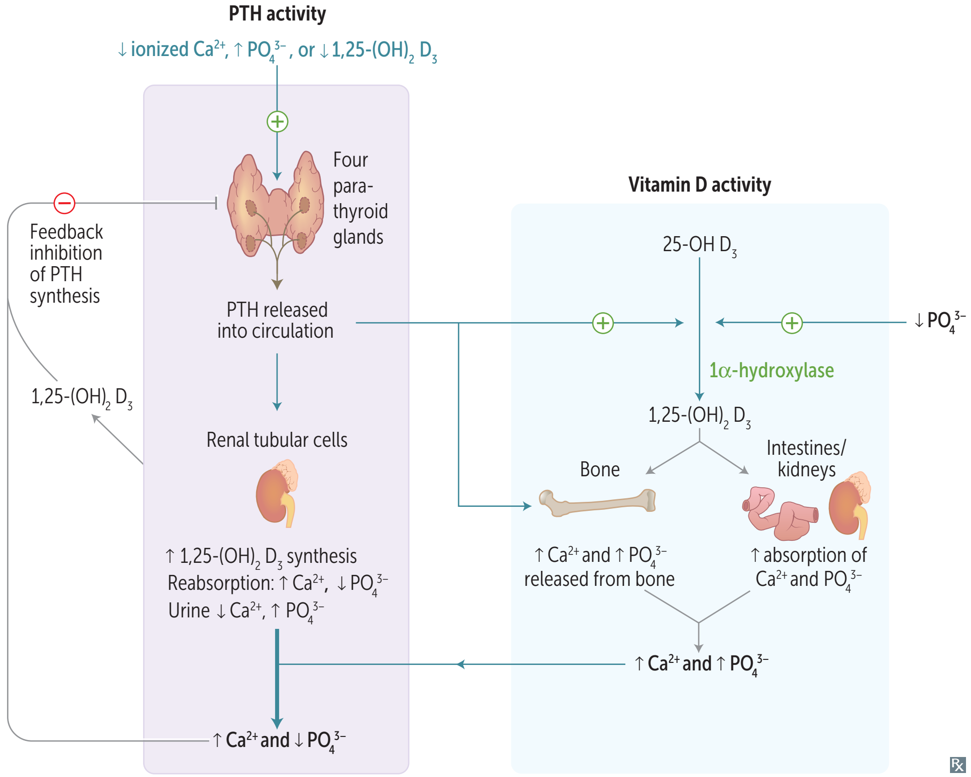
Plasma Ca^{2+} exists in three forms: - Ionized/free (~ 45%, active form) - Bound to albumin (~ 40%) - Bound to anions (~ 15%)	↑ in pH → ↑ affinity of albumin (↑ negative charge) to bind Ca^{2+} → hypocalcemia (cramps, pain, paresthesias, carpopedal spasm). Ionized/free Ca^{2+} is 1° regulator of PTH; changes in pH alter PTH secretion, whereas changes in albumin do not.

Vitamin D

SOURCE	D_3 from exposure of skin to sun, ingestion of fish and plants. D_2 from ingestion of plants, fungi, yeasts. Both converted to 25-OH in liver and to 1,25-$(OH)_2$ vitamin D (active form) in kidney.	Deficiency → rickets in kids, osteomalacia in adults. Caused by malabsorption, ↓ sunlight, poor diet, chronic kidney failure. 24,25-$(OH)_2$ D_3 is an inactive form of vitamin D. PTH leads to ↑ Ca^{2+} reabsorption and ↓ PO_4^{3-} reabsorption in the kidney, whereas 1,25-$(OH)_2$ D_3 leads to ↑ absorption of both Ca^{2+} and PO_4^{3-} in the gut.
FUNCTION	↑ absorption of dietary Ca^{2+} and PO_4^{3-}. Enhances bone mineralization.	
REGULATION	↑ PTH, ↓ Ca^{2+}, ↓ PO_4^{3-} → ↑ 1,25-$(OH)_2$ production. 1,25-$(OH)_2$ feedback inhibits its own production.	

Parathyroid hormone

SOURCE	Chief cells of parathyroid.	
FUNCTION	↑ bone resorption of Ca^{2+} and PO_4^{3-}. ↑ kidney reabsorption of Ca^{2+} in distal convoluted tubule. ↓ reabsorption of PO_4^{3-} in proximal convoluted tubule. ↑ 1,25-$(OH)_2$ D_3 (calcitriol) production by stimulating kidney 1α-hydroxylase in proximal convoluted tubule.	PTH ↑ serum Ca^{2+}, ↓ serum (PO_4^{3-}), ↑ urine (PO_4^{3-}), ↑ urine cAMP. ↑ RANK-L (receptor activator of NF-κB ligand) secreted by osteoblasts and osteocytes. Binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and ↑ Ca^{2+} → bone resorption. Intermittent PTH release can also stimulate bone formation. **PTH** = **P**hosphate-**T**rashing **H**ormone. PTH-related peptide (PTHrP) functions like PTH and is commonly increased in malignancies (eg, squamous cell carcinoma of the lung, renal cell carcinoma).
REGULATION	↓ serum Ca^{2+} → ↑ PTH secretion. ↑ serum PO_4^{3-} → ↑ PTH secretion. ↓ serum Mg^{2+} → ↑ PTH secretion. ↓↓ serum Mg^{2+} → ↓ PTH secretion. Common causes of ↓ Mg^{2+} include diarrhea, aminoglycosides, diuretics, alcohol abuse.	


PTH activity
↓ ionized Ca^{2+}, ↑ PO_4^{3-}, or ↓ 1,25-$(OH)_2$ D_3
+
Four para-thyroid glands
−
Feedback inhibition of PTH synthesis
PTH released into circulation
1,25-$(OH)_2$ D_3
Renal tubular cells
↑ 1,25-$(OH)_2$ D_3 synthesis
Reabsorption: ↑ Ca^{2+}, ↓ PO_4^{3-}
Urine ↓ Ca^{2+}, ↑ PO_4^{3-}
↑ Ca^{2+} and ↓ PO_4^{3-}
Vitamin D activity
25-OH D_3
+
+
↓ PO_4^{3-}
1α-hydroxylase
1,25-$(OH)_2$ D_3
Bone
Intestines/ kidneys
↑ Ca^{2+} and ↑ PO_4^{3-} released from bone
↑ absorption of Ca^{2+} and PO_4^{3-}
↑ Ca^{2+} and ↑ PO_4^{3-}

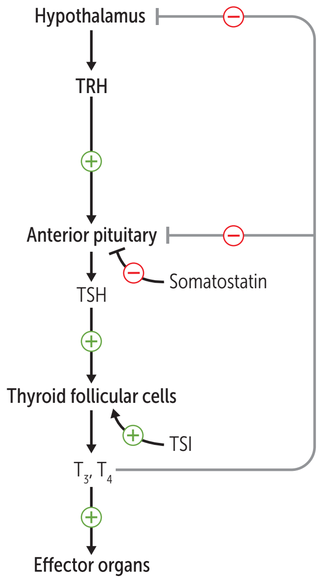
Calcitonin

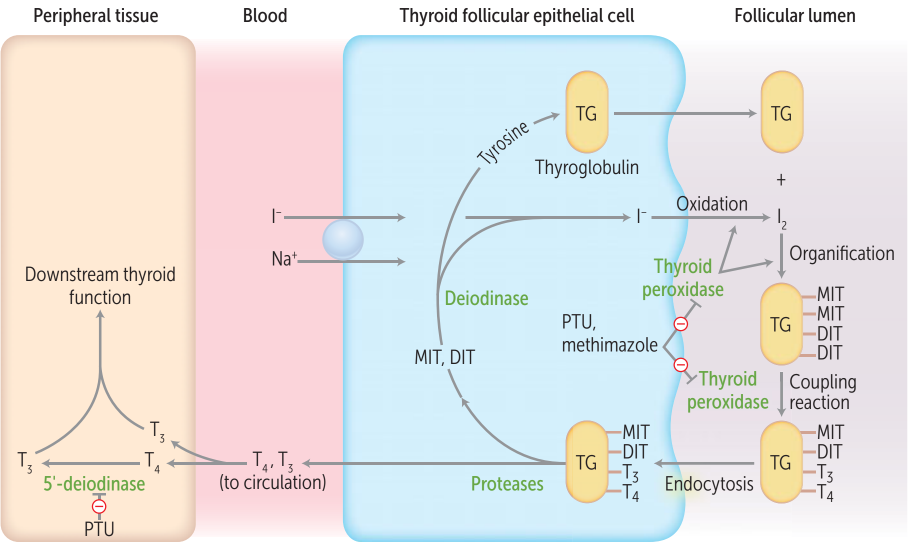
SOURCE	Parafollicular cells (C cells) of thyroid.	Calcitonin opposes actions of PTH. Not important in normal Ca^{2+} homeostasis. Calcitonin tones down serum Ca^{2+} levels and keeps it in bones.
FUNCTION	↓ bone resorption of Ca^{2+}.	
REGULATION	↑ serum Ca^{2+} → calcitonin secretion.	

Thyroid hormones (T_3/T_4)

Iodine-containing hormones that control the body's metabolic rate.

SOURCE	Follicles of thyroid. Most T_3 formed in target tissues.	T_3 functions—**4 B's**: **B**rain maturation **B**one growth **β**-adrenergic effects **B**asal metabolic rate ↑ Thyroxine-binding globulin (TBG) binds most T_3/T_4 in blood; only free hormone is active. ↓ TBG in hepatic failure, steroids; ↑ TBG in pregnancy or OCP use (estrogen ↑ TBG). T_4 is major thyroid product; converted to T_3 in peripheral tissue by 5′-deiodinase. T_3 binds nuclear receptor with greater affinity than T_4. Thyroid peroxidase is the enzyme responsible for oxidation and organification of iodide as well as coupling of monoiodotyrosine (MIT) and di-iodotyrosine (DIT). DIT + DIT = T_4. DIT + MIT = T_3. Propylthiouracil (PTU) inhibits both thyroid peroxidase and 5′-deiodinase. Methimazole inhibits thyroid peroxidase only. Glucocorticoids inhibit peripheral conversion of T_4 to T_3.
FUNCTION	Bone growth (synergism with GH) CNS maturation ↑ $β_1$ receptors in heart = ↑ CO, HR, SV, contractility ↑ basal metabolic rate via ↑ Na^+/K^+-ATPase activity → ↑ O_2 consumption, RR, body temperature ↑ glycogenolysis, gluconeogenesis, lipolysis	
REGULATION	TRH (hypothalamus) stimulates TSH (pituitary), which stimulates follicular cells. May also be stimulated by thyroid-stimulating immunoglobulin (TSI) in Graves disease. Negative feedback primarily by free T_3/T_4 to anterior pituitary (↓ sensitivity to TRH) and hypothalamus (↓ TRH secretion). Wolff-Chaikoff effect—excess iodine temporarily inhibits thyroid peroxidase → ↓ iodine organification → ↓ T_3/T_4 production.	


Hypothalamus
⊖
TRH
⊕
Anterior pituitary
⊖
⊖
Somatostatin
TSH
⊕
Thyroid follicular cells
⊕
TSI
T3, T4
⊕
Effector organs


Peripheral tissue
Blood
Thyroid follicular epithelial cell
Follicular lumen
Tyrosine
TG
Thyroglobulin
TG
+
I⁻
I⁻
Oxidation
I2
Na⁺
Organification
Thyroid peroxidase
Deiodinase
TG
MIT
MIT
DIT
DIT
PTU, methimazole
⊖
⊖
Thyroid peroxidase
Coupling reaction
MIT, DIT
Downstream thyroid function
T3
T4
T3
T4
5′-deiodinase
⊖
PTU
T4, T3
(to circulation)
Proteases
TG
MIT
DIT
T3
T4
Endocytosis
TG
MIT
DIT
T3
T4

Signaling pathways of endocrine hormones

cAMP	FSH, LH, ACTH, TSH, CRH, hCG, ADH (V_2-receptor), MSH, PTH, calcitonin, GHRH, glucagon, histamine (H_2-receptor)	FLAT ChAMP
cGMP	BNP, ANP, EDRF (NO)	BAD GraMPa Think vasodilators
IP_3	GnRH, Oxytocin, ADH (V_1-receptor), TRH, Histamine (H_1-receptor), Angiotensin II, Gastrin	GOAT HAG
Intracellular receptor	Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T_3/T_4, Vitamin D	PET CAT on TV
Receptor tyrosine kinase	Insulin, IGF-1, FGF, PDGF, EGF	MAP kinase pathway Think Growth Factors
Nonreceptor tyrosine kinase	Prolactin, Immunomodulators (eg, cytokines IL-2, IL-6, IFN), GH, G-CSF, Erythropoietin, Thrombopoietin	JAK/STAT pathway Think acidophils and cytokines PIGGLET

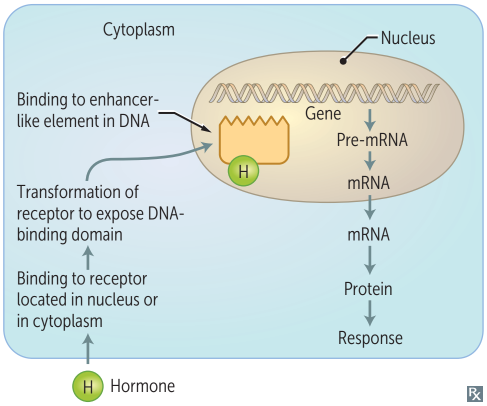
Signaling pathway of steroid hormones

Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which ↑ their solubility.

In men, ↑ sex hormone–binding globulin (SHBG) lowers free testosterone → gynecomastia.

In women, ↓ SHBG raises free testosterone → hirsutism.

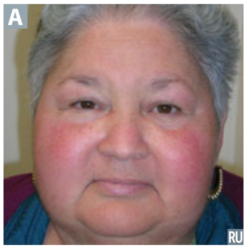
OCPs, pregnancy → ↑ SHBG.

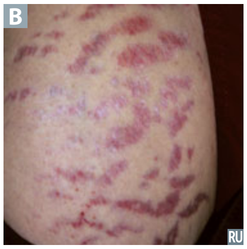

Cytoplasm
Nucleus
Binding to enhancer-like element in DNA
Gene
Pre-mRNA
H
mRNA
Transformation of receptor to expose DNA-binding domain
mRNA
Binding to receptor located in nucleus or in cytoplasm
Protein
Response
H
Hormone

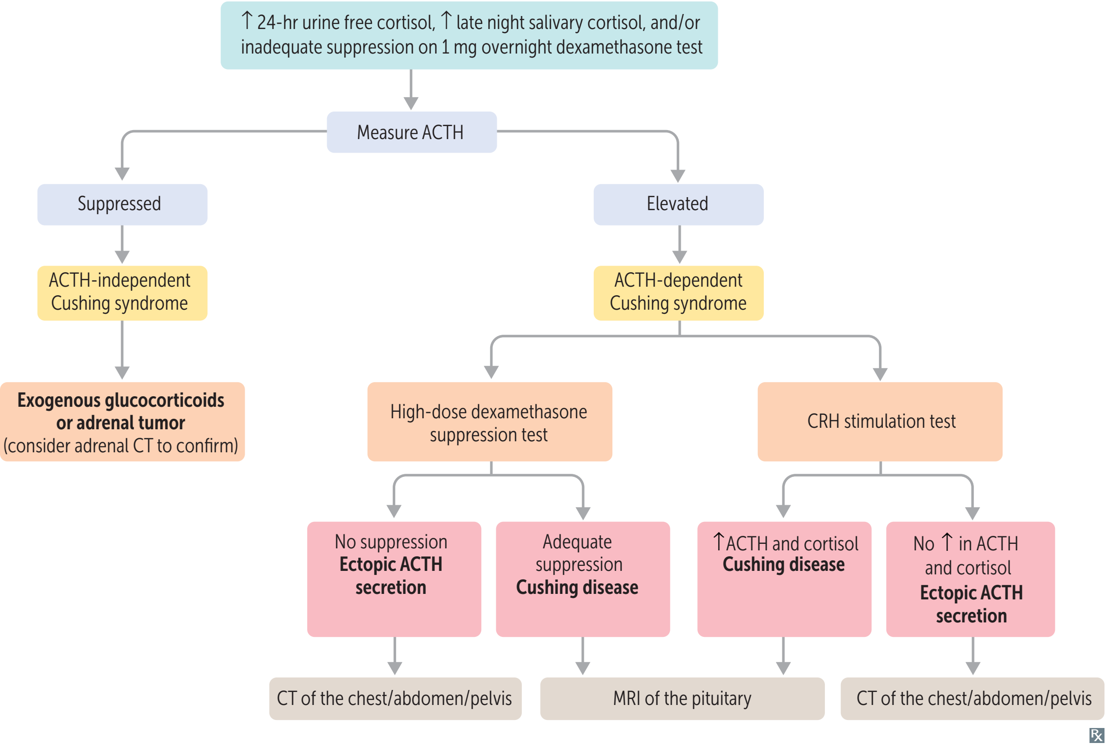
▸ ENDOCRINE—PATHOLOGY

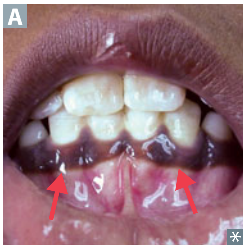
Cushing syndrome

ETIOLOGY	↑ cortisol due to a variety of causes: ▪ Exogenous corticosteroids—result in ↓ ACTH, bilateral adrenal atrophy. Most common cause. ▪ Primary adrenal adenoma, hyperplasia, or carcinoma—result in ↓ ACTH, atrophy of uninvolved adrenal gland. Can also present with pseudohyperaldosteronism. ▪ ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids)—result in ↑ ACTH, bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.
FINDINGS	Hypertension, weight gain, moon facies **A**, abdominal striae **B** and truncal obesity, buffalo hump, skin changes (eg, thinning, striae), osteoporosis, hyperglycemia (insulin resistance), amenorrhea, immunosuppression.
DIAGNOSIS	Screening tests include: ↑ free cortisol on 24-hr urinalysis, ↑ midnight salivary cortisol, and no suppression with overnight low-dose dexamethasone test. Measure serum ACTH. If ↓, suspect adrenal tumor or exogenous glucocorticoids. If ↑, distinguish between Cushing disease and ectopic ACTH secretion (eg, from small cell lung cancer) with a high-dose dexamethasone suppression test and CRH stimulation test. Ectopic secretion will not decrease with dexamethasone because the source is resistant to negative feedback; ectopic secretion will not increase with CRH because pituitary ACTH is suppressed.






↑ 24-hr urine free cortisol, ↑ late night salivary cortisol, and/or inadequate suppression on 1 mg overnight dexamethasone test
Measure ACTH
Suppressed
Elevated
ACTH-independent Cushing syndrome
ACTH-dependent Cushing syndrome
Exogenous glucocorticoids or adrenal tumor (consider adrenal CT to confirm)
High-dose dexamethasone suppression test
CRH stimulation test
No suppression Ectopic ACTH secretion
Adequate suppression Cushing disease
↑ACTH and cortisol Cushing disease
No ↑ in ACTH and cortisol Ectopic ACTH secretion
CT of the chest/abdomen/pelvis
MRI of the pituitary
CT of the chest/abdomen/pelvis
℞

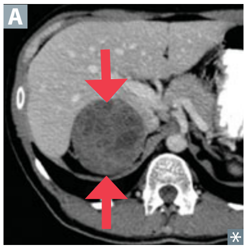
Adrenal insufficiency	Inability of adrenal glands to generate enough glucocorticoids +/– mineralocorticoids for the body's needs. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings. Treatment: glucocorticoid/mineralocorticoid replacement.	Diagnosis involves measurement of serum electrolytes, morning/random serum cortisol and ACTH (low cortisol, high ACTH in 1° adrenal insufficiency; low cortisol, low ACTH in 2°/3° adrenal insufficiency due to pituitary/hypothalamic disease), and response to ACTH stimulation test. Alternatively, can use metyrapone stimulation test: metyrapone blocks last step of cortisol synthesis (11-deoxycortisol → cortisol). Normal response is ↓ cortisol and compensatory ↑ ACTH and 11-deoxycortisol. In 1° adrenal insufficiency, ACTH is ↑ but 11-deoxycortisol remains ↓ after test. In 2°/3° adrenal insufficiency, both ACTH and 11-deoxycortisol remain ↓ after test.
Primary adrenal insufficiency 	Deficiency of aldosterone and cortisol production due to loss of gland function → hypotension (hyponatremic volume contraction), hyperkalemia, metabolic acidosis, skin and mucosal hyperpigmentation A (due to ↑ MSH, a byproduct of ACTH production from proopiomelanocortin [POMC]). ▪ **Acute**—sudden onset (eg, due to massive hemorrhage). May present with shock in acute adrenal crisis. ▪ **Chronic**—aka **Addison disease**. Due to adrenal atrophy or destruction by disease (autoimmune destruction most common in the Western world; TB most common in the developing world).	Primary Pigments the skin/mucosa. Associated with autoimmune polyglandular syndromes. **Waterhouse-Friderichsen syndrome**—acute 1° adrenal insufficiency due to adrenal hemorrhage associated with septicemia (usually *Neisseria meningitidis*), DIC, endotoxic shock.
Secondary adrenal insufficiency	Seen with ↓ pituitary ACTH production. No skin/mucosal hyperpigmentation, no hyperkalemia (aldosterone synthesis preserved due to intact renin-angiotensin-aldosterone axis).	Secondary Spares the skin/mucosa.
Tertiary adrenal insufficiency	Seen in patients with chronic exogenous steroid use, precipitated by abrupt withdrawal. Aldosterone synthesis unaffected.	Tertiary from Treatment.

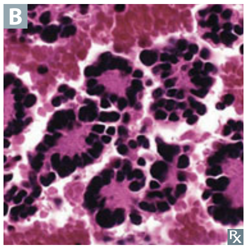
Hyperaldosteronism	Increased secretion of aldosterone from adrenal gland. Clinical features include hypertension, ↓ or normal K^+, metabolic alkalosis. No edema due to aldosterone escape mechanism.
Primary hyperaldosteronism	Seen with adrenal adenoma (Conn syndrome) or bilateral adrenal hyperplasia. ↑ aldosterone, ↓ renin.
Secondary hyperaldosteronism	Seen in patients with renovascular hypertension, juxtaglomerular cell tumors (renin-producing), and edema (eg, cirrhosis, heart failure, nephrotic syndrome).

Neuroendocrine tumors

Group of neoplasms originating from Kulchitsky and enterochromaffin-like cells. Occur in various organs (eg, thyroid: medullary carcinoma; lungs: small cell carcinoma; pancreas: islet cell tumor; adrenals: pheochromocytoma). Cells contain amine precursor uptake decarboxylase (APUD) and secrete different hormones (eg, 5-HIAA, neuron-specific enolase [NSE], chromogranin A).

Neuroblastoma



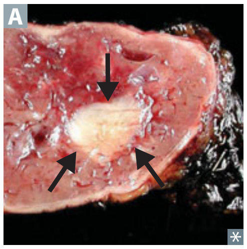


Most common tumor of the adrenal medulla A in **children,** usually < 4 years old. Originates from neural crest cells. Occurs anywhere along the sympathetic chain.

Most common presentation is abdominal distension and a firm, irregular mass that can cross the midline (vs Wilms tumor, which is smooth and unilateral). Less likely to develop hypertension than with pheochromocytoma. Can also present with opsoclonus-myoclonus syndrome ("dancing eyes-dancing feet").

↑ HVA and VMA (catecholamine metabolites) in urine. Homer-Wright rosettes B characteristic of neuroblastoma and medulloblastoma. Bombesin and NSE ⊕. Associated with overexpression of N-*myc* oncogene. Classified as an APUD tumor.

Pheochromocytoma

ETIOLOGY 	Most common tumor of the adrenal medulla in **adults** A. Derived from chromaffin cells (arise from neural crest). May be associated with germline mutations (eg, *NF-1*, *VHL*, *RET* [MEN 2A, 2B]).	**Rule of 10's**: 10% malignant 10% bilateral 10% extra-adrenal (eg, bladder wall, organ of Zuckerkandl) 10% calcify 10% kids
SYMPTOMS	Most tumors secrete epinephrine, norepinephrine, and dopamine, which can cause episodic hypertension. Symptoms occur in "spells"—relapse and remit.	Episodic hyperadrenergic symptoms (**5 P's**): Pressure (↑ BP) Pain (headache) Perspiration Palpitations (tachycardia) Pallor
FINDINGS	↑ catecholamines and metanephrines in urine and plasma.	
TREATMENT	Irreversible α-antagonists (eg, phenoxybenzamine) followed by β-blockers prior to tumor resection. α-blockade must be achieved before giving β-blockers to avoid a hypertensive crisis.	**Phenoxybenzamine** (16 letters) is given for **pheochromocytoma** (also 16 letters).

Hypothyroidism vs hyperthyroidism

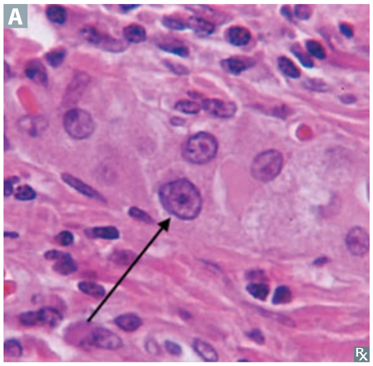
	Hypothyroidism	Hyperthyroidism
SIGNS/SYMPTOMS	Cold intolerance (↓ heat production)	Heat intolerance (↑ heat production)
	Weight gain, ↓ appetite	Weight loss, ↑ appetite
	Hypoactivity, lethargy, fatigue, weakness, depressed mood	Hyperactivity, anxiety, insomnia, hand tremor
	Constipation	Diarrhea/hyperdefecation
	↓ reflexes (delayed/slow relaxing)	↑ reflexes (brisk)
	Hypothyroid myopathy (proximal muscle weakness, ↑ CK)	Thyrotoxic myopathy (proximal muscle weakness, normal CK)
	Myxedema (facial/periorbital)	Pretibial myxedema (Graves disease), periorbital edema
	Dry, cool skin; coarse, brittle hair	Warm, moist skin; fine hair
	Bradycardia, dyspnea on exertion	Chest pain, palpitations, and arrhythmias (eg, atrial fibrillation) due to ↑ number and sensitivity of β-adrenergic receptors
LAB FINDINGS	↑ TSH (if 1°)	↓ TSH (if 1°)
	↓ free T_3 and T_4	↑ free or total T_3 and T_4
	Hypercholesterolemia (due to ↓ LDL receptor expression)	Hypocholesterolemia (due to ↑ LDL receptor expression)

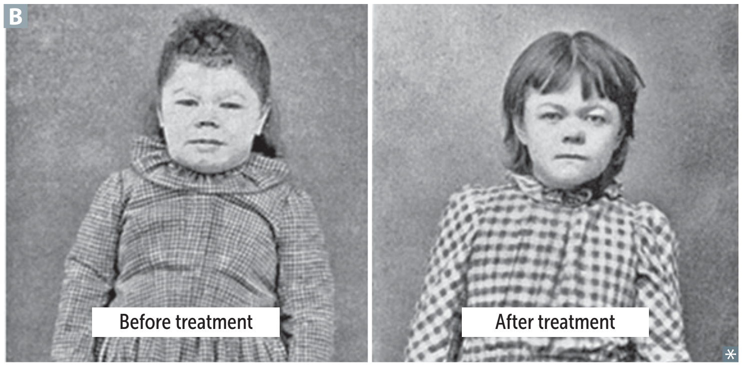
Causes of goiter

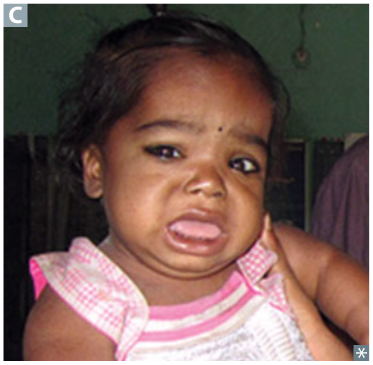
Smooth/diffuse	Nodular
Graves disease	Toxic multinodular goiter
Hashimoto thyroiditis	Thyroid adenoma
Iodine deficiency	Thyroid cancer
TSH-secreting pituitary adenoma	Thyroid cyst

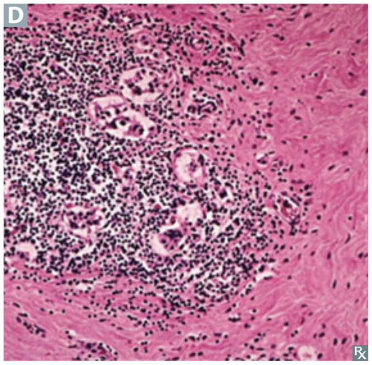
Hypothyroidism

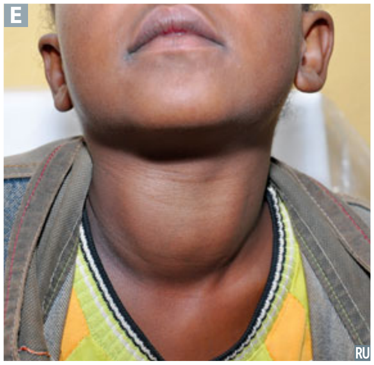
Hashimoto thyroiditis	Most common cause of hypothyroidism in iodine-sufficient regions; an autoimmune disorder with antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies. Associated with ↑ risk of non-Hodgkin lymphoma (typically of B-cell origin). May be hyperthyroid early in course due to thyrotoxicosis during follicular rupture. Histologic findings: Hürthle cells, lymphoid aggregates with germinal centers A. Findings: moderately enlarged, **nontender** thyroid.
Congenital hypothyroidism (cretinism)	Severe fetal hypothyroidism due to maternal hypothyroidism, thyroid agenesis, thyroid dysgenesis (most common cause in US), iodine deficiency, dyshormonogenetic goiter. Findings: Pot-bellied, Pale, Puffy-faced child with Protruding umbilicus, Protuberant tongue, and Poor brain development: the 6 P's B C.
Subacute granulomatous thyroiditis (de Quervain)	Self-limited disease often following a flu-like illness (eg, viral infection). May be hyperthyroid early in course, followed by hypothyroidism. Histology: granulomatous inflammation. Findings: ↑ ESR, jaw pain, very **tender** thyroid. (de Quervain is associated with pain.)
Riedel thyroiditis	Thyroid replaced by fibrous tissue with inflammatory infiltrate D. Fibrosis may extend to local structures (eg, trachea, esophagus), mimicking anaplastic carcinoma. ⅓ are hypothyroid. Considered a manifestation of IgG$_4$-related systemic disease (eg, autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis). Findings: fixed, hard (rock-like), **painless** goiter.
Other causes	Iodine deficiency E, goitrogens (eg, amiodarone, lithium), Wolff-Chaikoff effect (thyroid gland downregulation in response to ↑ iodide).





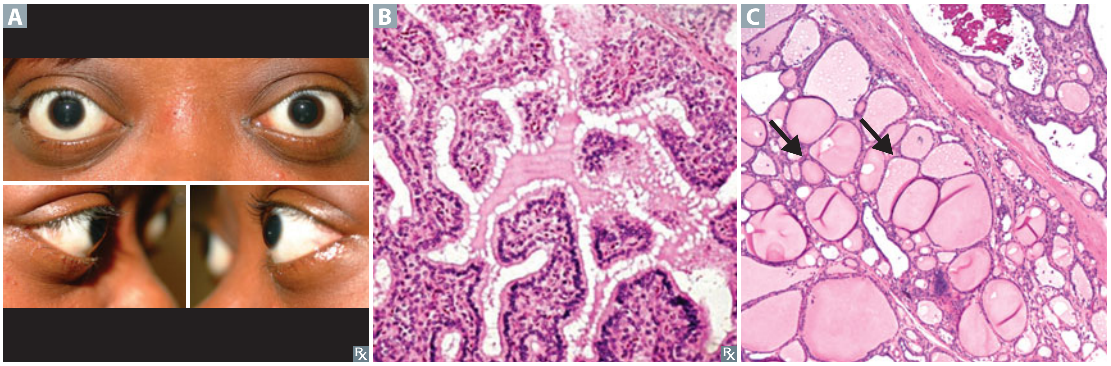


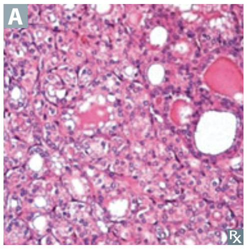
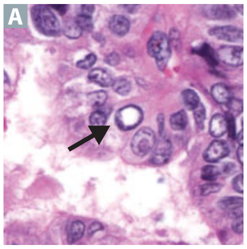
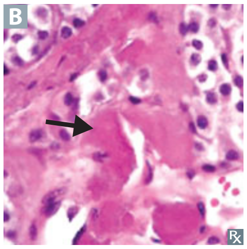




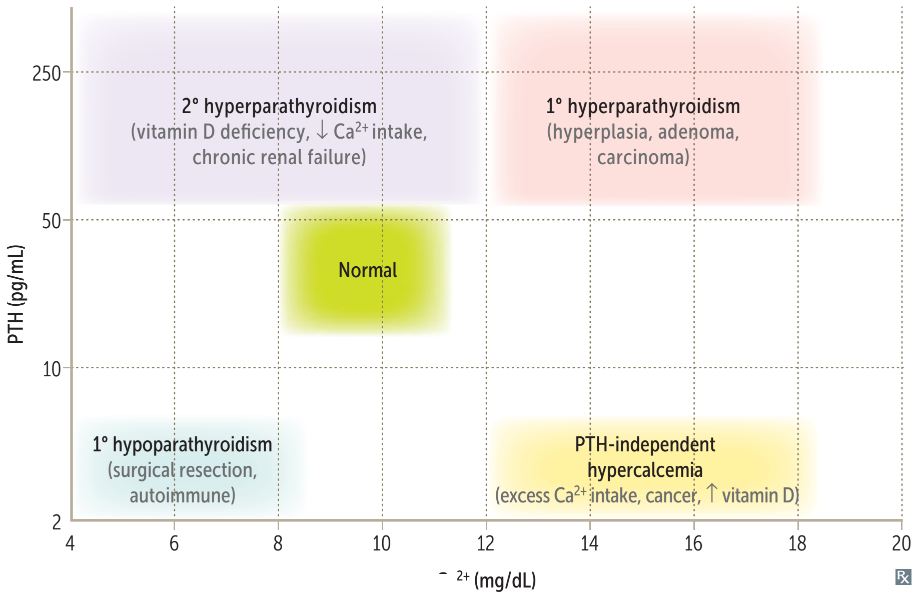
Hyperthyroidism

Graves disease	Most common cause of hyperthyroidism. Thyroid-stimulating immunoglobulin (IgG; type II hypersensitivity) stimulates TSH receptors on thyroid (hyperthyroidism, diffuse goiter) and dermal fibroblasts (pretibial myxedema). Infiltration of retroorbital space by activated T-cells → ↑ cytokines (eg, TNF-α, IFN-γ) → ↑ fibroblast secretion of hydrophilic GAGs → ↑ osmotic muscle swelling, muscle inflammation, and adipocyte count → exophthalmos A. Often presents during stress (eg, pregnancy). Associated with HLA-DR3 and HLA-B8. Tall, crowded follicular epithelial cells; scalloped colloid B.
Toxic multinodular goiter	Focal patches of hyperfunctioning follicular cells distended with colloid C working independently of TSH (due to TSH receptor mutations in 60% of cases). ↑ release of T_3 and T_4. Hot nodules are rarely malignant.
Thyroid storm	Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery. Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May see ↑ LFTs. Treat with the 4 P's: β-blockers (eg, Propranolol), Propylthiouracil, corticosteroids (eg, Prednisolone), Potassium iodide (Lugol iodine).
Jod-Basedow phenomenon	Thyrotoxicosis if a patient with iodine deficiency and partially autonomous thyroid tissue (eg, autonomous nodule) is made iodine replete. Opposite of Wolff-Chaikoff effect.



Thyroid adenoma  	Benign solitary growth of the thyroid. Most are nonfunctional ("cold"), can rarely cause hyperthyroidism via autonomous thyroid hormone production ("hot" or "toxic"). Most common histology is follicular A; absence of capsular or vascular invasion (unlike follicular carcinoma).
Thyroid cancer	Typically diagnosed with fine needle aspiration; treated with thyroidectomy. Complications of surgery include hoarseness (due to recurrent laryngeal nerve damage), hypocalcemia (due to removal of parathyroid glands), and transection of recurrent and superior laryngeal nerves (during ligation of inferior thyroid artery and superior laryngeal artery, respectively).
Papillary carcinoma  	Most common, excellent prognosis. Empty-appearing nuclei with central clearing ("**Orphan Annie**" eyes) A, psam**Moma** bodies, nuclear grooves (**Papi** and **Moma** adopted **Orphan Annie**). ↑ risk with *RET* and *BRAF* mutations, childhood irradiation.
Follicular carcinoma	Good prognosis. Invades thyroid capsule and vasculature (unlike follicular adenoma), uniform follicles; hematogenous spread is common. Associated with *RAS* mutation.
Medullary carcinoma  	From parafollicular "C cells"; produces calcitonin, sheets of cells in an amyloid stroma (stains with Congo red B). Associated with MEN 2A and 2B (*RET* mutations).
Undifferentiated/ anaplastic carcinoma	Older patients; invades local structures, very poor prognosis.
Lymphoma	Associated with Hashimoto thyroiditis.

Diagnosis of parathyroid disease



Hypoparathyroidism

Due to accidental surgical excision of parathyroid glands, autoimmune destruction, or DiGeorge syndrome. Findings: tetany, hypocalcemia, hyperphosphatemia.

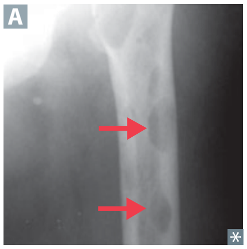
Chvostek sign—tapping of facial nerve (tap the **Ch**eek) → contraction of facial muscles.

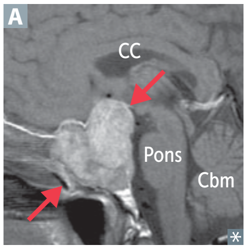
Trousseau sign—occlusion of brachial artery with BP cuff (cuff the **Tr**iceps) → carpal spasm.

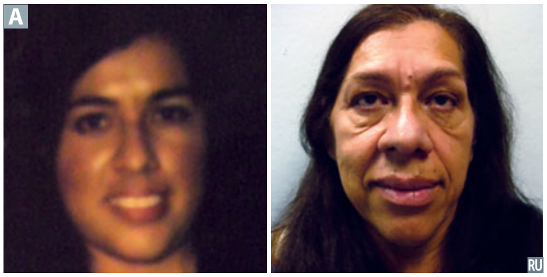
Pseudohypoparathyroidism type 1A (Albright hereditary osteodystrophy)—unresponsiveness of kidney to PTH → hypocalcemia despite ↑ PTH levels. Characterized by shortened 4th/5th digits, short stature. Autosomal dominant. Due to defective G_s protein α-subunit causing end-organ resistance to PTH. Defect must be inherited from mother due to imprinting.

Pseudopseudohypoparathyroidism—physical exam features of Albright hereditary osteodystrophy but without end-organ PTH resistance (PTH level normal). Occurs when defective G_s protein α-subunit is inherited from father.

Hyperparathyroidism

Primary hyperparathyroidism 	Usually due to parathyroid adenoma or hyperplasia. **Hypercalcemia**, hypercalciuria (renal **stones**), polyuria (**thrones**), hypophosphatemia, ↑ PTH, ↑ ALP, ↑ cAMP in urine. Most often asymptomatic. May present with weakness and constipation ("**groans**"), abdominal/flank pain (kidney stones, acute pancreatitis), depression ("**psychiatric overtones**").	**Osteitis fibrosa cystica**—cystic **bone** spaces filled with brown fibrous tissue A ("brown tumor" consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain). Due to ↑ PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism). "**Stones**, **thrones**, **bones**, **groans**, and **psychiatric overtones**."
Secondary hyperparathyroidism	2° hyperplasia due to ↓ Ca^{2+} absorption and/or ↑ PO_4^{3-}, most often in chronic renal disease (causes hypovitaminosis D and hyperphosphatemia → ↓ Ca^{2+}). **Hypocalcemia**, hyperphosphatemia in chronic renal failure (vs hypophosphatemia with most other causes), ↑ ALP, ↑ PTH.	**Renal osteodystrophy**—renal disease → 2° and 3° hyperparathyroidism → bone lesions.
Tertiary hyperparathyroidism	Refractory (autonomous) hyperparathyroidism resulting from chronic renal disease. ↑↑ PTH, ↑ Ca^{2+}.	

Familial hypocalciuric hypercalcemia	Defective G-coupled Ca^{2+}-sensing receptors in multiple tissues (eg, parathyroids, kidneys). Higher than normal Ca^{2+} levels required to suppress PTH. Excessive renal Ca^{2+} reuptake → mild hypercalcemia and hypocalciuria with normal to ↑ PTH levels.
Pituitary adenoma 	Benign tumor, most commonly prolactinoma (arises from lactotrophs). Adenoma A may be functional (hormone producing) or nonfunctional (silent). Nonfunctional tumors present with mass effect (bitemporal hemianopia, hypopituitarism, headache). Functional tumor presentation is based on the hormone produced. Prolactinoma in women classically presents as galactorrhea, amenorrhea, and ↓ bone density due to suppression of estrogen. Prolactinoma in men classically presents as low libido and infertility. Treatment: dopamine agonists (eg, bromocriptine, cabergoline), transsphenoidal resection.
Nelson syndrome	Enlargement of existing ACTH-secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease (due to removal of cortisol feedback mechanism). Presents with hyperpigmentation, headaches and bitemporal hemianopia. Treatment: pituitary irradiation or surgical resection.

Acromegaly	Excess GH in adults. Typically caused by pituitary adenoma.	
FINDINGS	Large tongue with deep furrows, deep voice, large hands and feet, coarsening of facial features with aging A, frontal bossing, diaphoresis (excessive sweating), impaired glucose tolerance (insulin resistance). ↑ risk of colorectal polyps and cancer.	↑ GH in children → gigantism (↑ linear bone growth). HF most common cause of death. 
DIAGNOSIS	↑ serum IGF-1; failure to suppress serum GH following oral glucose tolerance test; pituitary mass seen on brain MRI.	
TREATMENT	Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog) or pegvisomant (growth hormone receptor antagonist), dopamine agonists (eg, cabergoline).	

Laron syndrome (dwarfism)	Defective growth hormone receptors → ↓ linear growth. ↑ GH, ↓ IGF-1. Clinical features include short height, small head circumference, characteristic facies with saddle nose and prominent forehead, delayed skeletal maturation, small genitalia.

Diabetes insipidus

Characterized by intense thirst and polyuria with inability to concentrate urine due to lack of ADH (central) or failure of response to circulating ADH (nephrogenic).

	Central DI	Nephrogenic DI
ETIOLOGY	Pituitary tumor, autoimmune, trauma, surgery, ischemic encephalopathy, idiopathic	Hereditary (ADH receptor mutation), 2° to hypercalcemia, hypokalemia, lithium, demeclocycline (ADH antagonist)
FINDINGS	↓ ADH Urine specific gravity < 1.006 Serum osmolality > 290 mOsm/kg Hyperosmotic volume contraction	Normal or ↑ ADH levels Urine specific gravity < 1.006 Serum osmolality > 290 mOsm/kg Hyperosmotic volume contraction
WATER DEPRIVATION TEST[a]	$> 50\%$ ↑ in urine osmolality only after administration of ADH analog	Minimal change in urine osmolality, even after administration of ADH analog
TREATMENT	Desmopressin acetate Hydration	HCTZ, indomethacin, amiloride Hydration, dietary salt restriction, avoidance of offending agent

[a] No water intake for 2–3 hr followed by hourly measurements of urine volume and osmolarity and plasma Na^+ concentration and osmolarity. ADH analog (desmopressin acetate) is administered if serum osmolality $> 295–300$ mOsm/kg, plasma $Na^+ \geq 145$, or urine osmolality does not rise despite a rising plasma osmolality.

Syndrome of inappropriate antidiuretic hormone secretion

Characterized by:
- Excessive free water retention
- Euvolemic hyponatremia with continued urinary Na^+ excretion
- Urine osmolality > serum osmolality

Body responds to water retention with ↓ aldosterone and ↑ ANP and BNP → ↑ urinary Na^+ secretion → normalization of extracellular fluid volume → euvolemic hyponatremia. Very low serum Na^+ levels can lead to cerebral edema, seizures. Correct slowly to prevent osmotic demyelination syndrome (formerly known as central pontine myelinolysis).

SIADH causes include:
- Ectopic ADH (eg, small cell lung cancer)
- CNS disorders/head trauma
- Pulmonary disease
- Drugs (eg, cyclophosphamide)

Treatment: fluid restriction, salt tablets, IV hypertonic saline, diuretics, conivaptan, tolvaptan, demeclocycline.

Increased urine osmolality during water deprivation test indicates psychogenic polydipsia.

Hypopituitarism

Undersecretion of pituitary hormones due to:

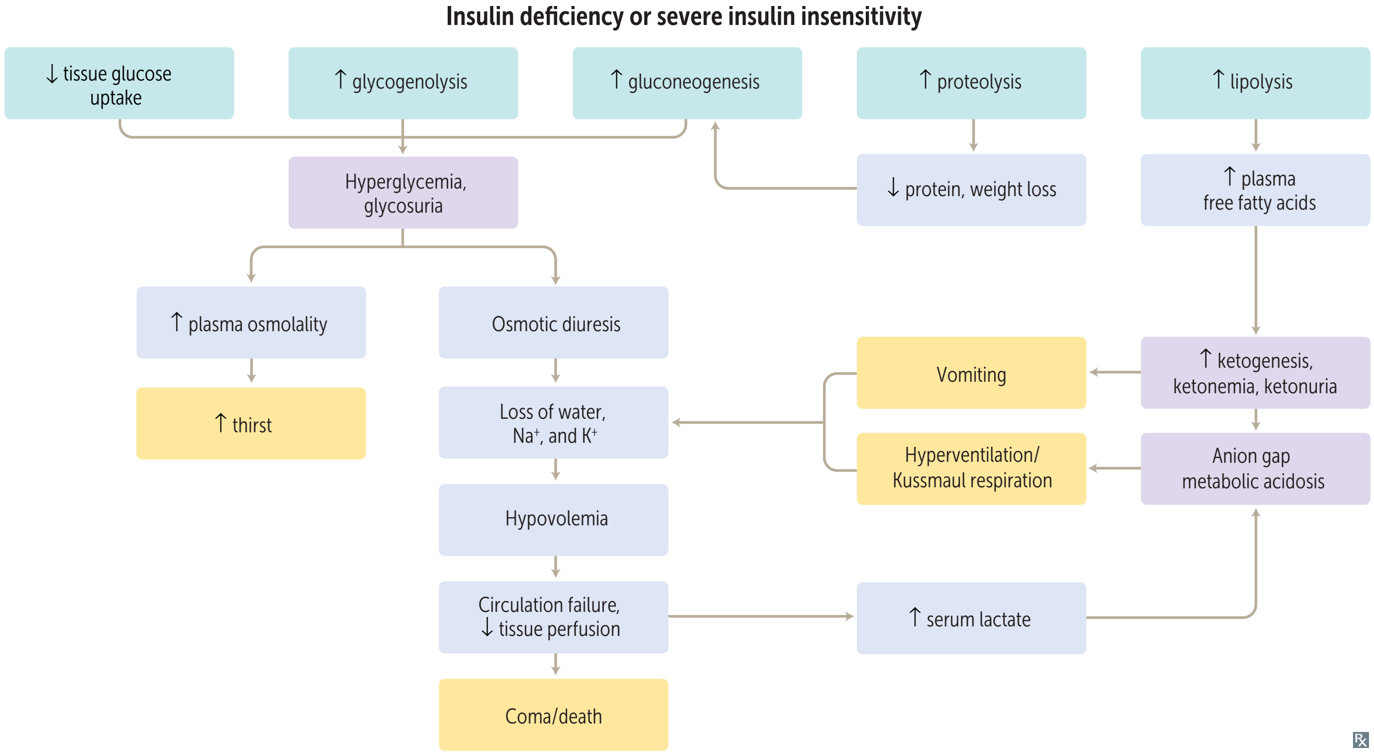
- Nonsecreting pituitary adenoma, craniopharyngioma
- **Sheehan syndrome**—ischemic infarct of pituitary following postpartum bleeding; pregnancy-induced pituitary growth → ↑ susceptibility to hypoperfusion. Usually presents with failure to lactate, absent menstruation, cold intolerance
- **Empty sella syndrome**—atrophy or compression of pituitary (which lies in the sella turcica), often idiopathic, common in obese women
- **Pituitary apoplexy**—sudden hemorrhage of pituitary gland, often in the presence of an existing pituitary adenoma. Usually presents with sudden onset severe headache, visual impairment (eg, bitemporal hemianopia, diplopia due to CN III palsy), and features of hypopituitarism.
- Brain injury
- Radiation

Treatment: hormone replacement therapy (corticosteroids, thyroxine, sex steroids, human growth hormone).

Diabetes mellitus

ACUTE MANIFESTATIONS	Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar coma (type 2). Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).
CHRONIC COMPLICATIONS	Nonenzymatic glycation: ▪ Small vessel disease (diffuse thickening of basement membrane) → retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, neuropathy, nephropathy (nodular glomerulosclerosis, aka Kimmelstiel-Wilson nodules → progressive proteinuria [initially microalbuminuria; ACE inhibitors are renoprotective] and arteriolosclerosis → hypertension; both lead to chronic renal failure). ▪ Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease, gangrene → limb loss, cerebrovascular disease. MI most common cause of death. Osmotic damage (sorbitol accumulation in organs with aldose reductase and ↓ or absent sorbitol dehydrogenase): ▪ Neuropathy (motor, sensory [glove and stocking distribution], and autonomic degeneration) ▪ Cataracts

DIAGNOSIS	TEST	DIAGNOSTIC CUTOFF	NOTES
	HbA_{1c}	≥ 6.5%	Reflects average blood glucose over prior 3 months
	Fasting plasma glucose	≥ 126 mg/dL	Fasting for > 8 hours
	2-hour oral glucose tolerance test	≥ 200 mg/dL	2 hours after consumption of 75 g of glucose in water


Insulin deficiency or severe insulin insensitivity
↓ tissue glucose uptake
↑ glycogenolysis
↑ gluconeogenesis
↑ proteolysis
↑ lipolysis
Hyperglycemia, glycosuria
↓ protein, weight loss
↑ plasma free fatty acids
↑ plasma osmolality
Osmotic diuresis
↑ thirst
Loss of water, Na⁺, and K⁺
Vomiting
Hyperventilation/ Kussmaul respiration
↑ ketogenesis, ketonemia, ketonuria
Anion gap metabolic acidosis
Hypovolemia
Circulation failure, ↓ tissue perfusion
↑ serum lactate
Coma/death

Type 1 vs type 2 diabetes mellitus

Variable	Type 1	Type 2
1° DEFECT	Autoimmune destruction of β cells (eg, due to glutamic acid decarboxylase antibodies)	↑ resistance to insulin, progressive pancreatic β-cell failure
INSULIN NECESSARY IN TREATMENT	Always	Sometimes
AGE (EXCEPTIONS COMMONLY OCCUR)	< 30 yr	> 40 yr
ASSOCIATION WITH OBESITY	No	Yes
GENETIC PREDISPOSITION	Relatively weak (50% concordance in identical twins), polygenic	Relatively strong (90% concordance in identical twins), polygenic
ASSOCIATION WITH HLA SYSTEM	Yes (HLA-DR3 and -DR4)	No
GLUCOSE INTOLERANCE	Severe	Mild to moderate
INSULIN SENSITIVITY	High	Low
KETOACIDOSIS	Common	Rare
β-CELL NUMBERS IN THE ISLETS	↓	Variable (with amyloid deposits)
SERUM INSULIN LEVEL	↓	Variable
CLASSIC SYMPTOMS OF POLYURIA, POLYDIPSIA, POLYPHAGIA, WEIGHT LOSS	Common	Sometimes
HISTOLOGY	Islet leukocytic infiltrate	Islet amyloid polypeptide (IAPP) deposits

Diabetic ketoacidosis	One of the most feared complications of diabetes. Usually due to insulin noncompliance or ↑ insulin requirements from ↑ stress (eg, infection). Excess fat breakdown and ↑ ketogenesis from ↑ free fatty acids, which are then made into ketone bodies (β-hydroxybutyrate > acetoacetate). Usually occurs in type 1 diabetes, as endogenous insulin in type 2 diabetes usually prevents lipolysis.
SIGNS/SYMPTOMS	**DKA** is **D**eadly: **D**elirium/psychosis, **K**ussmaul respirations (rapid/deep breathing), **A**bdominal pain/nausea/vomiting, **D**ehydration. Fruity breath odor (due to exhaled acetone).
LABS	Hyperglycemia, ↑ H^+, ↓ HCO_3^- (↑ anion gap metabolic acidosis), ↑ blood ketone levels, leukocytosis. Hyperkalemia, but depleted intracellular K^+ due to transcellular shift from ↓ insulin and acidosis (therefore total body K^+ is depleted).
COMPLICATIONS	Life-threatening mucormycosis (usually caused by *Rhizopus* infection), cerebral edema, cardiac arrhythmias, heart failure.
TREATMENT	IV fluids, IV insulin, and K^+ (to replete intracellular stores); glucose if necessary to prevent hypoglycemia.

Hyperosmolar hyperglycemic state

State of profound hyperglycemia-induced dehydration and ↑ serum osmolality, classically seen in elderly type 2 diabetics with limited ability to drink. Hyperglycemia → excessive osmotic diuresis → dehydration → eventual onset of HHNS. Symptoms: thirst, polyuria, lethargy, focal neurological deficits (eg, seizures), can progress to coma and death if left untreated. Labs: hyperglycemia (often > 600 mg/dL), ↑ serum osmolality (> 320 mOsm/kg), no acidosis (pH > 7.3, ketone production inhibited by presence of insulin). Treatment: aggressive IV fluids, insulin therapy.

Glucagonoma

Tumor of pancreatic α cells → overproduction of glucagon. Presents with dermatitis (necrolytic migratory erythema), diabetes (hyperglycemia), DVT, declining weight, depression. Treatment: octreotide, surgery.

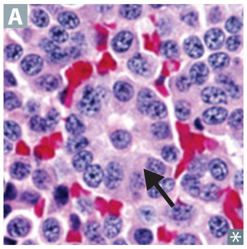
Insulinoma

Tumor of pancreatic β cells → overproduction of insulin → hypoglycemia. May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of glucose levels. Symptomatic patients have ↓ blood glucose and ↑ C-peptide levels (vs exogenous insulin use). ~ 10% of cases associated with MEN 1 syndrome. Treatment: surgical resection.

Somatostatinoma

Tumor of pancreatic δ cells → overproduction of somatostatin → ↓ secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP). May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria. Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

Carcinoid syndrome



Rare syndrome caused by carcinoid tumors (neuroendocrine cells A; note prominent rosettes [arrow]), especially metastatic small bowel tumors, which secrete high levels of serotonin (5-HT). Not seen if tumor is limited to GI tract (5-HT undergoes first-pass metabolism in liver). Results in recurrent diarrhea, cutaneous flushing, asthmatic wheezing, right-sided valvular heart disease (tricuspid regurgitation, pulmonic stenosis). ↑ 5-hydroxyindoleacetic acid (5-HIAA) in urine, niacin deficiency (pellagra).

Treatment: surgical resection, somatostatin analog (eg, octreotide).

Rule of 1/3s:
- 1/3 metastasize
- 1/3 present with 2nd malignancy
- 1/3 are multiple

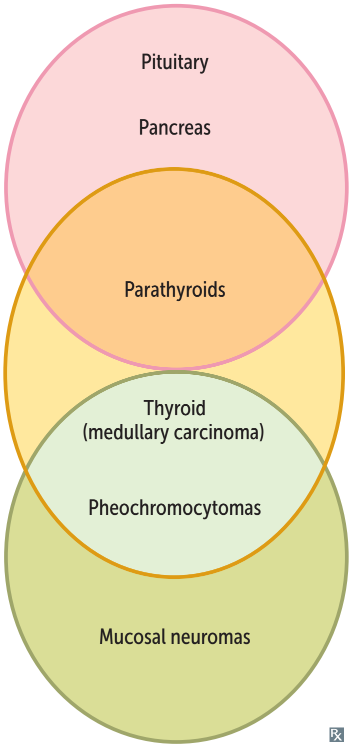
Most common malignancy in the small intestine.

Zollinger-Ellison syndrome

Gastrin-secreting tumor (gastrinoma) of pancreas or duodenum. Acid hypersecretion causes recurrent ulcers in duodenum and jejunum. Presents with abdominal pain (peptic ulcer disease, distal ulcers), diarrhea (malabsorption). Positive secretin stimulation test: gastrin levels remain elevated after administration of secretin, which normally inhibits gastrin release. May be associated with MEN 1.

Multiple endocrine neoplasias

All **MEN** syndromes have autosomal **dominant** inheritance.
"All **MEN** are **dominant**" (or so they think).

SUBTYPE	CHARACTERISTICS	COMMENTS
MEN 1	**P**ituitary tumors (prolactin or GH) **P**ancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare) **P**arathyroid adenomas Associated with mutation of *MEN1* (menin, a tumor suppressor, chromosome 11)	 Pituitary Pancreas Parathyroids Thyroid (medullary carcinoma) Pheochromocytomas Mucosal neuromas
MEN 2A	**P**arathyroid hyperplasia Medullary thyroid carcinoma—neoplasm of parafollicular or C cells; secretes calcitonin; prophylactic thyroidectomy required **P**heochromocytoma (secretes catecholamines) Associated with mutation in *RET* (codes for receptor tyrosine kinase) in cells of neural crest origin	
MEN 2B	Medullary thyroid carcinoma **P**heochromocytoma Mucosal neuromas (oral/intestinal ganglioneuromatosis) Associated with marfanoid habitus; mutation in *RET* gene	MEN 1 = **3 P's**: **P**ituitary, **P**arathyroid, and **P**ancreas MEN 2A = **2 P's**: **P**arathyroids and **P**heochromocytoma MEN 2B = **1 P**: **P**heochromocytoma

▶ ENDOCRINE—PHARMACOLOGY

Diabetes mellitus management

Treatment strategies:

- Type 1 DM—dietary modifications, insulin replacement
- Type 2 DM—dietary modifications and exercise for weight loss; oral agents, non-insulin injectables, insulin replacement
- Gestational DM (GDM)—dietary modifications, exercise, insulin replacement if lifestyle modification fails

DRUG CLASSES	CLINICAL USE	ACTION	RISKS/CONCERNS
Insulin preparations			
Insulin, rapid acting Lispro, aspart, glulisine	Type 1 DM, type 2 DM, GDM (postprandial glucose control).	Binds insulin receptor (tyrosine kinase activity). Liver: ↑ glucose stored as glycogen. Muscle: ↑ glycogen, protein synthesis; ↑ K^+ uptake. Fat: ↑ TG storage.	Hypoglycemia, lipodystrophy, rare hypersensitivity reactions.
Insulin, short acting Regular	Type 1 DM, type 2 DM, GDM, DKA (IV), hyperkalemia (+ glucose), stress hyperglycemia.		
Insulin, intermediate acting NPH	Type 1 DM, type 2 DM, GDM.		
Insulin, long acting Detemir, glargine	Type 1 DM, type 2 DM, GDM (basal glucose control).		
Oral drugs			
Biguanides Metformin	Oral. First-line therapy in type 2 DM, causes modest weight loss. Can be used in patients without islet function.	Inhibit hepatic gluconeogenesis and the action of glucagon. ↓ gluconeogenesis, ↑ glycolysis, ↑ peripheral glucose uptake (↑ insulin sensitivity).	GI upset; most serious adverse effect is lactic acidosis (thus contraindicated in renal insufficiency).
Sulfonylureas First generation: chlorpropamide, tolbutamide Second generation: glimepiride, glipizide, glyburide	Stimulate release of endogenous insulin in type 2 DM. Require some islet function, so useless in type 1 DM.	Close K^+ channel in β cell membrane → cell depolarizes → insulin release via ↑ Ca^{2+} influx.	Risk of hypoglycemia ↑ in renal failure, weight gain. First generation: disulfiram-like effects. Second generation: hypoglycemia.
Glitazones/ thiazolidinediones Pioglitazone, rosiglitazone	Used as monotherapy in type 2 DM or combined with above agents. Safe to use in renal impairment.	↑ insulin sensitivity in peripheral tissue. Binds to PPAR-γ nuclear transcription regulator.[a]	Weight gain, edema, HF, ↑ risk of fractures.

Diabetes mellitus management *(continued)*

DRUG CLASSES	CLINICAL USE	ACTION	RISKS/CONCERNS
Oral hypoglycemic drugs *(continued)*			
Meglitinides Nateglinide, repaglinide	Used as monotherapy in type 2 DM or combined with metformin.	Stimulate postprandial insulin release by binding to K^+ channels on β cell membranes (site differs from sulfonylureas).	Hypoglycemia (↑ risk with renal failure), weight gain.
GLP-1 analogs Exenatide, liraglutide (sc injection)	Type 2 DM.	↑ glucose-dependent insulin release, ↓ glucagon release, ↓ gastric emptying, ↑ satiety.	Nausea, vomiting, pancreatitis; modest weight loss.
DPP-4 inhibitors Linagliptin, saxagliptin, sitagliptin	Type 2 DM.	Inhibit DPP-4 enzyme that deactivates GLP-1, thereby ↑ glucose-dependent insulin release, ↓ glucagon release, ↓ gastric emptying, ↑ satiety.	Mild urinary or respiratory infections; weight neutral.
Amylin analogs Pramlintide (sc injection)	Type 1 DM, type 2 DM.	↓ gastric emptying, ↓ glucagon.	Hypoglycemia (in setting of mistimed prandial insulin), nausea.
Sodium-glucose co-transporter 2 (SGLT2) inhibitors Canagliflozin, dapagliflozin, empagliflozin	Type 2 DM.	Block reabsorption of glucose in PCT.	Glucosuria, UTIs, vaginal yeast infections, hyperkalemia, dehydration (orthostatic hypotension), weight loss.
α-glucosidase inhibitors Acarbose, miglitol	Type 2 DM.	Inhibit intestinal brush-border α-glucosidases. Delayed carbohydrate hydrolysis and glucose absorption → ↓ postprandial hyperglycemia.	GI disturbances.

[a] Genes activated by PPAR-γ regulate fatty acid storage and glucose metabolism. Activation of PPAR-γ ↑ insulin sensitivity and levels of adiponectin.

Thioamides	Propylthiouracil, methimazole.
MECHANISM	Block thyroid peroxidase, inhibiting the oxidation of iodide and the organification and coupling of iodine → inhibition of thyroid hormone synthesis. Propylthiouracil also blocks 5′-deiodinase → ↓ peripheral conversion of T_4 to T_3.
CLINICAL USE	Hyperthyroidism. PTU blocks Peripheral conversion. PTU used in first trimester of pregnancy (due to methimazole teratogenicity); methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity).
ADVERSE EFFECTS	Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity. Methimazole is a possible teratogen (can cause aplasia cutis).

Levothyroxine, triiodothyronine

MECHANISM	Thyroid hormone replacement.
CLINICAL USE	Hypothyroidism, myxedema. Used off-label as weight loss supplements.
ADVERSE EFFECTS	Tachycardia, heat intolerance, tremors, arrhythmias.

Hypothalamic/pituitary drugs

DRUG	CLINICAL USE
ADH antagonists (conivaptan, tolvaptan)	SIADH, block action of ADH at V_2-receptor.
Desmopressin acetate	Central (not nephrogenic) DI, von Willebrand disease, sleep enuresis.
GH	GH deficiency, Turner syndrome.
Oxytocin	Stimulates labor, uterine contractions, milk let-down; controls uterine hemorrhage.
Somatostatin (octreotide)	Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices.

Demeclocycline

MECHANISM	ADH antagonist (member of tetracycline family).
CLINICAL USE	SIADH.
ADVERSE EFFECTS	Nephrogenic DI, photosensitivity, abnormalities of bone and teeth.

Fludrocortisone

MECHANISM	Synthetic analog of aldosterone with little glucocorticoid effects.
CLINICAL USE	Mineralocorticoid replacement in 1° adrenal insufficiency.
ADVERSE EFFECTS	Similar to glucocorticoids; also edema, exacerbation of heart failure, hyperpigmentation.

Cinacalcet

MECHANISM	Sensitizes Ca^{2+}-sensing receptor (CaSR) in parathyroid gland to circulating Ca^{2+} → ↓ PTH.
CLINICAL USE	1° or 2° hyperparathyroidism.
ADVERSE EFFECTS	Hypocalcemia.

HIGH-YIELD SYSTEMS

Gastrointestinal

"A good set of bowels is worth more to a man than any quantity of brains."
—Josh Billings

"Man should strive to have his intestines relaxed all the days of his life."
—Moses Maimonides

"Is life worth living? It all depends on the liver."
—William James

- Embryology 344
- Anatomy 345
- Physiology 356
- Pathology 359
- Pharmacology 381

▸ GASTROINTESTINAL—EMBRYOLOGY

Normal gastrointestinal embryology

Foregut—esophagus to upper duodenum.
Midgut—lower duodenum to proximal $^2/_3$ of transverse colon.
Hindgut—distal $^1/_3$ of transverse colon to anal canal above pectinate line.
Midgut development:

- 6th week—physiologic midgut herniates through umbilical ring
- 10th week—returns to abdominal cavity + rotates around superior mesenteric artery (SMA), total 270° counterclockwise

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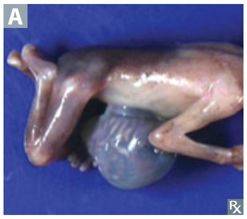
Ventral wall defects and hernias



Developmental defects due to failure of:

- Rostral fold closure—sternal defects (ectopia cordis)
- Lateral fold closure—omphalocele, gastroschisis
- Caudal fold closure—bladder exstrophy

Gastroschisis—extrusion of abdominal contents through abdominal folds (typically right of umbilicus); not covered by peritoneum or amnion.

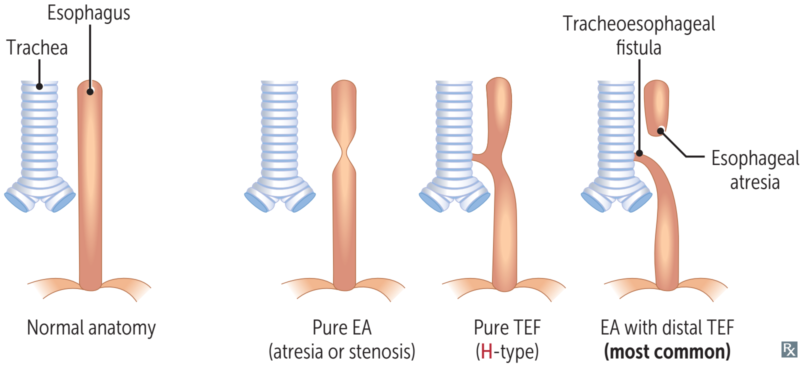
Omphalocele—persistent herniation of abdominal contents into umbilical cord, sealed by peritoneum A.

Congenital umbilical hernia—incomplete closure of umbilical ring. Many close spontaneously.

Tracheoesophageal anomalies

Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%). Polyhydramnios in utero. Neonates drool, choke, and vomit with first feeding. TEF allows air to enter stomach (visible on CXR). Cyanosis is 2° to laryngospasm (to avoid reflux-related aspiration). Clinical test: failure to pass nasogastric tube into stomach.

In H-type, the fistula resembles the letter H. In pure EA the CXR shows gasless abdomen.



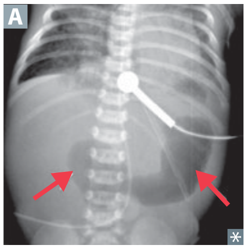
Normal anatomy

Pure EA (atresia or stenosis)

Pure TEF (H-type)

EA with distal TEF **(most common)**

Intestinal atresia



Presents with bilious vomiting and abdominal distension within first 1–2 days of life.

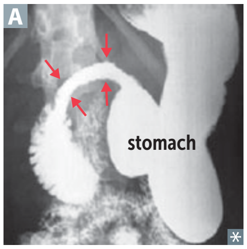
Duodenal atresia—failure to recanalize. Associated with "double bubble" (dilated stomach, proximal duodenum) on x-ray A. Associated with Down syndrome.

Jejunal and ileal atresia—disruption of mesenteric vessels → ischemic necrosis → segmental resorption (bowel discontinuity or "apple peel").

Hypertrophic pyloric stenosis

Most common cause of gastric outlet obstruction in infants (1:600). Palpable olive-shaped mass in epigastric region, visible peristaltic waves, and nonbilious projectile vomiting at ~ 2–6 weeks old. More common in firstborn males; associated with exposure to macrolides. Results in hypokalemic hypochloremic metabolic alkalosis (2° to vomiting of gastric acid and subsequent volume contraction). Treatment is surgical incision (pyloromyotomy).

Pancreas and spleen embryology

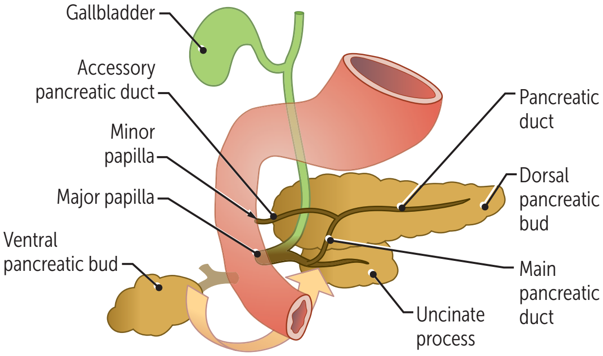


Pancreas—derived from foregut. Ventral pancreatic buds contribute to uncinate process and main pancreatic duct. The dorsal pancreatic bud alone becomes the body, tail, isthmus, and accessory pancreatic duct. Both the ventral and dorsal buds contribute to pancreatic head.

Annular pancreas—ventral pancreatic bud abnormally encircles 2nd part of duodenum; forms a ring of pancreatic tissue that may cause duodenal narrowing **A** and vomiting.

Pancreas divisum—ventral and dorsal parts fail to fuse at 8 weeks. Common anomaly; mostly asymptomatic, but may cause chronic abdominal pain and/or pancreatitis.

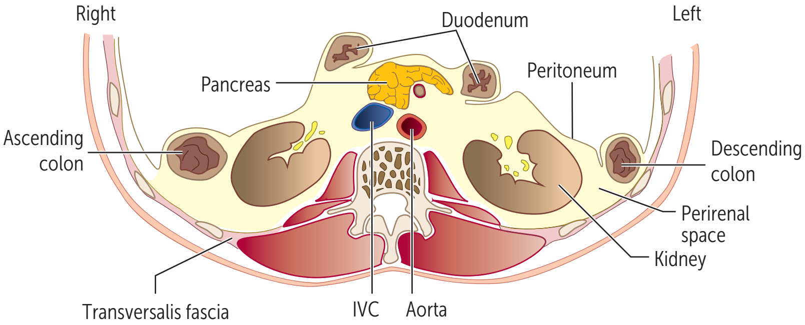
Spleen—arises in mesentery of stomach (hence is mesodermal) but has foregut supply (celiac trunk → splenic artery).


Gallbladder
Accessory pancreatic duct
Minor papilla
Major papilla
Ventral pancreatic bud
Pancreatic duct
Dorsal pancreatic bud
Main pancreatic duct
Uncinate process

▸ GASTROINTESTINAL—ANATOMY

Retroperitoneal structures

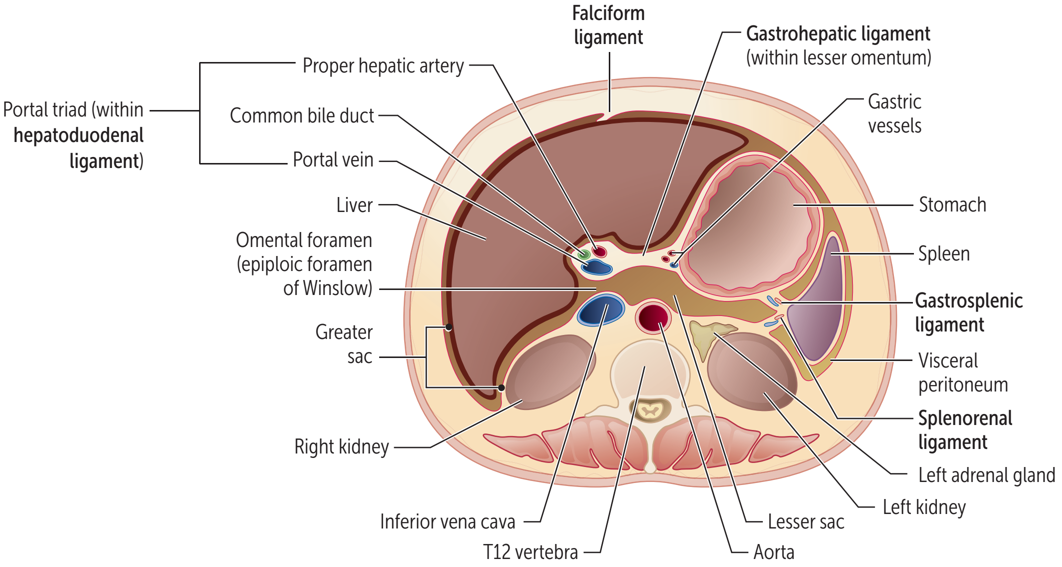
Retroperitoneal structures include GI structures that lack a mesentery and non-GI structures. Injuries to retroperitoneal structures can cause blood or gas accumulation in retroperitoneal space.


Right
Duodenum
Left
Peritoneum
Pancreas
Ascending colon
Descending colon
Perirenal space
Kidney
Transversalis fascia
IVC
Aorta

SAD PUCKER:

- **S**uprarenal (adrenal) glands [not shown]
- **A**orta and IVC
- **D**uodenum (2nd through 4th parts)
- **P**ancreas (except tail)
- **U**reters [not shown]
- **C**olon (descending and ascending)
- **K**idneys
- **E**sophagus (thoracic portion) [not shown]
- **R**ectum (partially) [not shown]

Important gastrointestinal ligaments


Falciform ligament
Gastrohepatic ligament (within lesser omentum)
Proper hepatic artery
Portal triad (within hepatoduodenal ligament)
Common bile duct
Portal vein
Gastric vessels
Liver
Stomach
Omental foramen (epiploic foramen of Winslow)
Spleen
Gastrosplenic ligament
Greater sac
Visceral peritoneum
Splenorenal ligament
Right kidney
Left adrenal gland
Left kidney
Inferior vena cava
Lesser sac
T12 vertebra
Aorta

LIGAMENT	CONNECTS	STRUCTURES CONTAINED	NOTES
Falciform	Liver to anterior abdominal wall	Ligamentum teres hepatis (derivative of fetal umbilical vein)	Derivative of ventral mesentery
Hepatoduodenal	Liver to duodenum	Portal triad: proper hepatic artery, portal vein, common bile duct	Pringle maneuver—ligament may be compressed between thumb and index finger placed in omental foramen to control bleeding Borders the omental foramen, which connects the greater and lesser sacs Part of lesser omentum
Gastrohepatic	Liver to lesser curvature of stomach	Gastric arteries	Separates greater and lesser sacs on the right May be cut during surgery to access lesser sac Part of lesser omentum
Gastrocolic (not shown)	Greater curvature and transverse colon	Gastroepiploic arteries	Part of greater omentum
Gastrosplenic	Greater curvature and spleen	Short gastrics, left gastroepiploic vessels	Separates greater and lesser sacs on the left Part of greater omentum
Splenorenal	Spleen to posterior abdominal wall	Splenic artery and vein, tail of pancreas	

Digestive tract anatomy

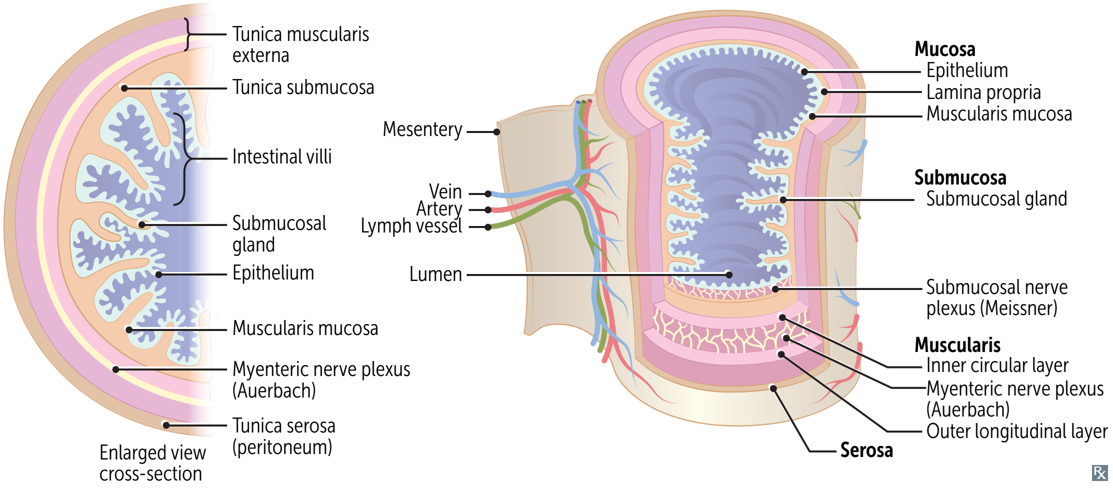
Layers of gut wall (inside to outside—MSMS):

- Mucosa—epithelium, lamina propria, muscularis mucosa
- Submucosa—includes Submucosal nerve plexus (Meissner), Secretes fluid
- Muscularis externa—includes Myenteric nerve plexus (Auerbach), Motility
- Serosa (when intraperitoneal), adventitia (when retroperitoneal)

Ulcers can extend into submucosa, inner or outer muscular layer. Erosions are in the mucosa only.

Frequencies of basal electric rhythm (slow waves):

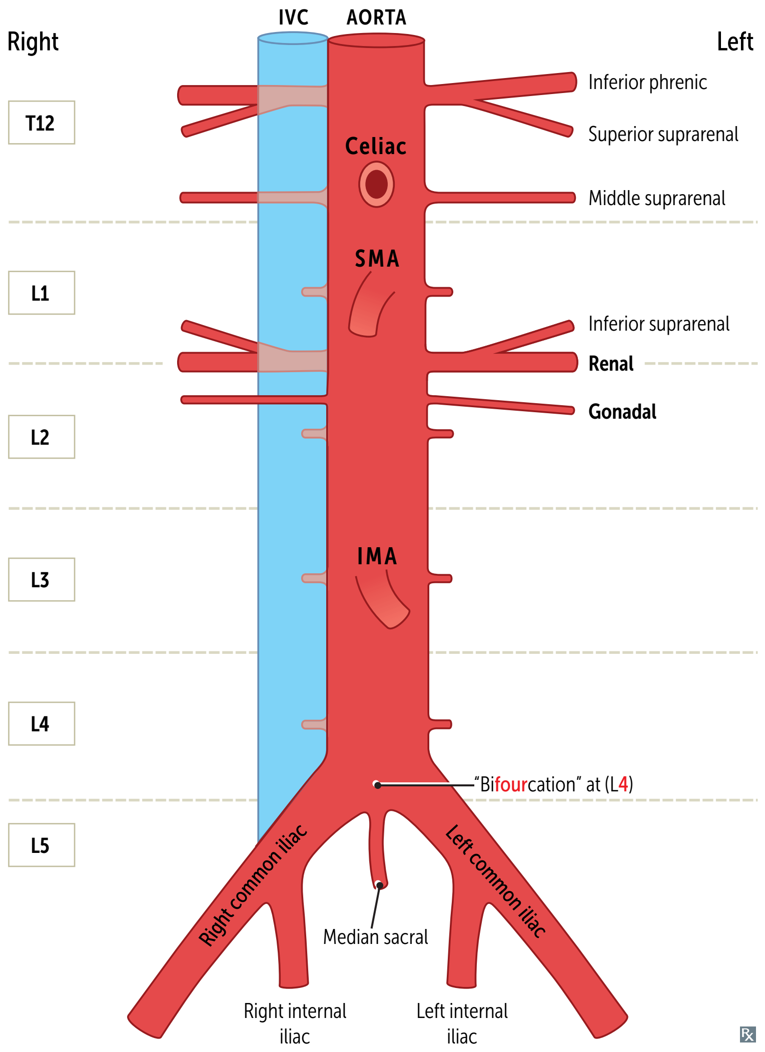
- Stomach—3 waves/min
- Duodenum—12 waves/min
- Ileum—8–9 waves/min


Tunica muscularis externa
Tunica submucosa
Intestinal villi
Submucosal gland
Epithelium
Muscularis mucosa
Myenteric nerve plexus (Auerbach)
Tunica serosa (peritoneum)
Enlarged view cross-section
Mesentery
Vein
Artery
Lymph vessel
Lumen
Mucosa
Epithelium
Lamina propria
Muscularis mucosa
Submucosa
Submucosal gland
Submucosal nerve plexus (Meissner)
Muscularis
Inner circular layer
Myenteric nerve plexus (Auerbach)
Outer longitudinal layer
Serosa

Digestive tract histology

Esophagus	Nonkeratinized stratified squamous epithelium.
Stomach	Gastric glands.
Duodenum	Villi and microvilli ↑ absorptive surface. Brunner glands (HCO_3^--secreting cells of submucosa) and crypts of Lieberkühn (contain stem cells that replace enterocytes/goblet cells and Paneth cells that secrete defensins, lysozyme, and TNF).
Jejunum	Plicae circulares (also present in distal duodenum) and crypts of Lieberkühn.
Ileum	Peyer patches (lymphoid aggregates in lamina propria, submucosa), plicae circulares (proximal ileum), and crypts of Lieberkühn. Largest number of goblet cells in the small intestine.
Colon	Crypts of Lieberkühn but no villi; abundant goblet cells.

Abdominal aorta and branches


IVC
AORTA
Right
Left
T12
L1
L2
L3
L4
L5
Inferior phrenic
Superior suprarenal
Celiac
Middle suprarenal
SMA
Inferior suprarenal
Renal
Gonadal
IMA
"Bifourcation" at (L4)
Right common iliac
Left common iliac
Median sacral
Right internal iliac
Left internal iliac

Arteries supplying GI structures branch **anteriorly**. Arteries supplying non-GI structures branch **laterally** and **posteriorly**.

Superior mesenteric artery syndrome—Characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when transverse (third) portion of duodenum is compressed between SMA and aorta. Typically occurs in conditions associated with diminished mesenteric fat (eg, low body weight/malnutrition).

Gastrointestinal blood supply and innervation

EMBRYONIC GUT REGION	ARTERY	PARASYMPATHETIC INNERVATION	VERTEBRAL LEVEL	STRUCTURES SUPPLIED
Foregut	Celiac	Vagus	T12/L1	Pharynx (vagus nerve only) and lower esophagus (celiac artery only) to proximal duodenum; liver, gallbladder, pancreas, spleen (mesoderm)
Midgut	SMA	Vagus	L1	Distal duodenum to proximal $^2/_3$ of transverse colon
Hindgut	IMA	Pelvic	L3	Distal $^1/_3$ of transverse colon to upper portion of rectum

Celiac trunk

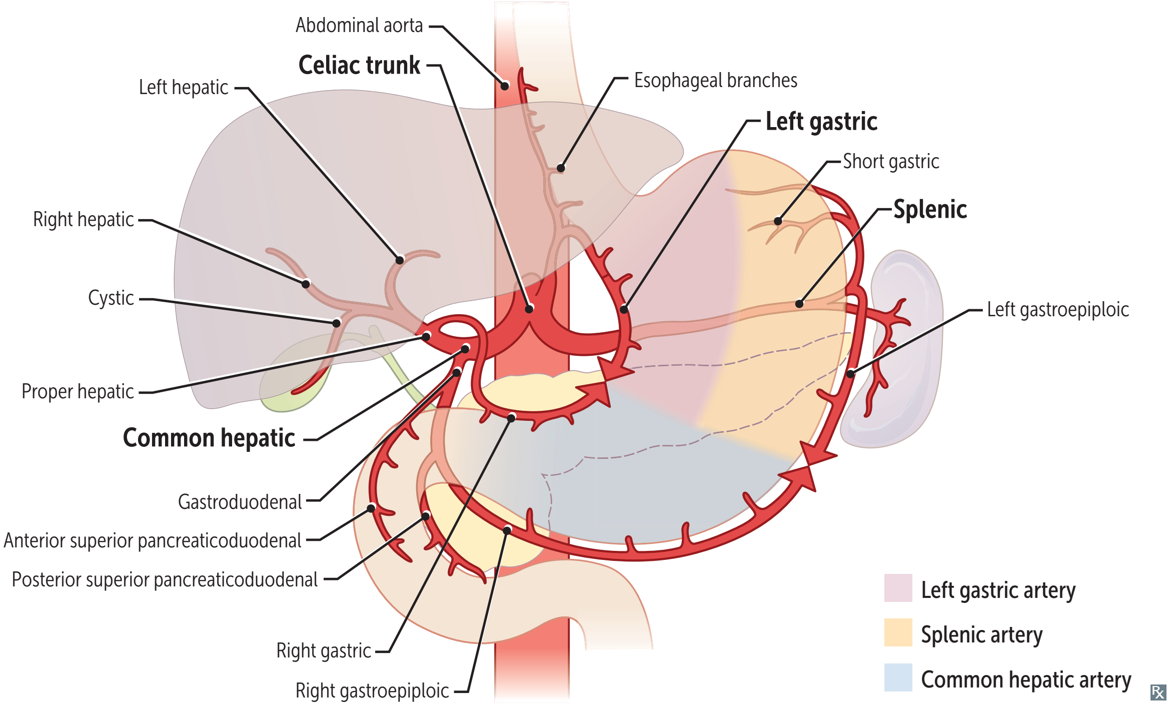
Branches of celiac trunk: common hepatic, splenic, and left gastric. These constitute the main blood supply of the stomach.

Strong anastomoses exist between:

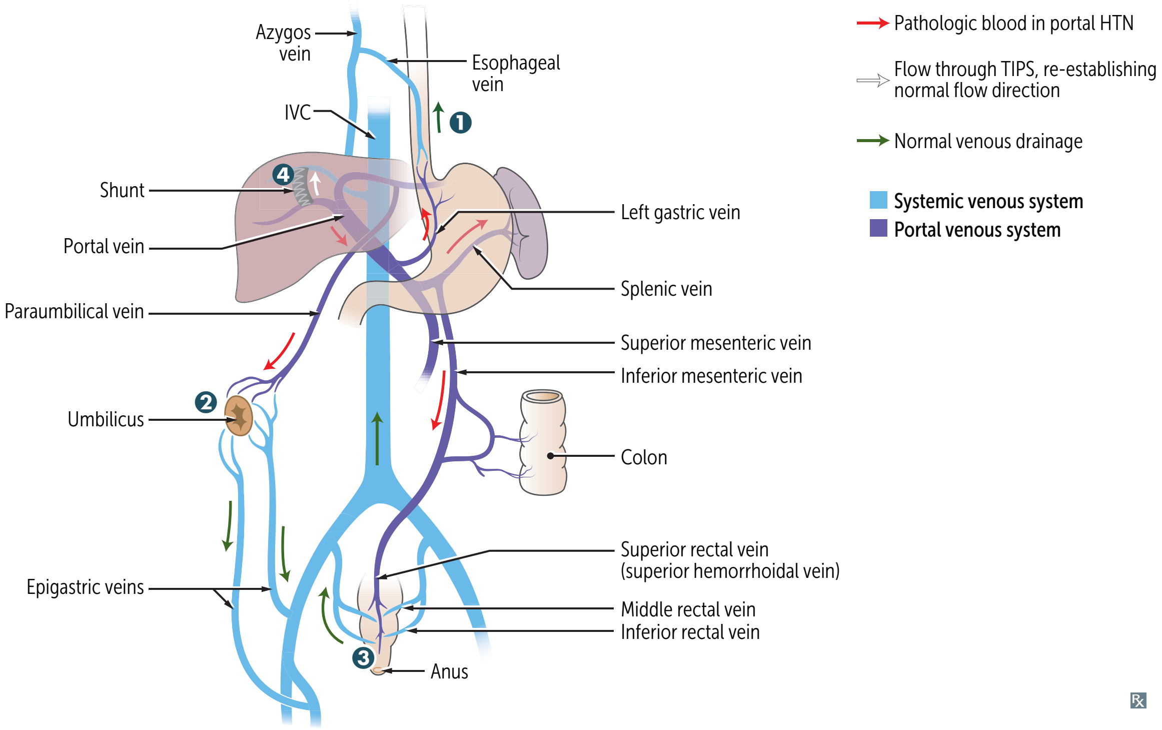
- Left and right gastroepiploics
- Left and right gastrics

Posterior duodenal ulcers penetrate gastroduodenal artery causing hemorrhage.

Anterior duodenal ulcers perforate into the anterior abdominal cavity, potentially leading to pneumoperitoneum.


Abdominal aorta
Celiac trunk
Left hepatic
Esophageal branches
Left gastric
Short gastric
Splenic
Right hepatic
Cystic
Left gastroepiploic
Proper hepatic
Common hepatic
Gastroduodenal
Anterior superior pancreaticoduodenal
Posterior superior pancreaticoduodenal
Right gastric
Right gastroepiploic
Left gastric artery
Splenic artery
Common hepatic artery
℞

Portosystemic anastomoses



Azygos vein
Esophageal vein
IVC
❶
Shunt
❹
Portal vein
Paraumbilical vein
Left gastric vein
Splenic vein
Superior mesenteric vein
Inferior mesenteric vein
❷
Umbilicus
Colon
Epigastric veins
Superior rectal vein (superior hemorrhoidal vein)
Middle rectal vein
Inferior rectal vein
❸
Anus
Pathologic blood in portal HTN
Flow through TIPS, re-establishing normal flow direction
Normal venous drainage
Systemic venous system
Portal venous system

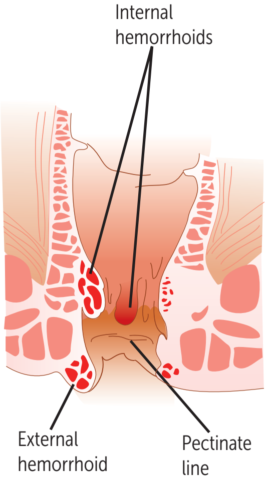
SITE OF ANASTOMOSIS	CLINICAL SIGN	PORTAL ↔ SYSTEMIC
❶ Esophagus	Esophageal varices	Left gastric ↔ azygos
❷ Umbilicus	Caput medusae	Paraumbilical ↔ small epigastric veins of the anterior abdominal wall.
❸ Rectum	Anorectal varices	Superior rectal ↔ middle and inferior rectal

Varices of gut, butt, and caput (medusae) are commonly seen with portal hypertension.

❹ Treatment with a transjugular intrahepatic portosystemic shunt (TIPS) between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver. Can precipitate hepatic encephalopathy.

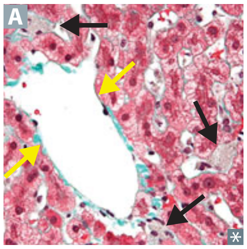
Pectinate (dentate) line

Formed where endoderm (hindgut) meets ectoderm.



Above pectinate line—internal hemorrhoids, adenocarcinoma. Arterial supply from superior rectal artery (branch of IMA). Venous drainage: superior rectal vein → inferior mesenteric vein → splenic vein → portal vein.	Internal hemorrhoids receive visceral innervation and are therefore **not painful**. Lymphatic drainage to internal iliac lymph nodes.
Below pectinate line—external hemorrhoids, anal fissures, squamous cell carcinoma. Arterial supply from inferior rectal artery (branch of internal pudendal artery). Venous drainage: inferior rectal vein → internal pudendal vein → internal iliac vein → common iliac vein → IVC.	External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore **painful** if thrombosed. Lymphatic drainage to superficial inguinal nodes. **Anal fissure**—tear in the anal mucosa below the Pectinate line. Pain while Pooping; blood on toilet Paper. Located Posteriorly because this area is Poorly Perfused. Associated with low-fiber diets and constipation.

Liver tissue architecture



Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids.

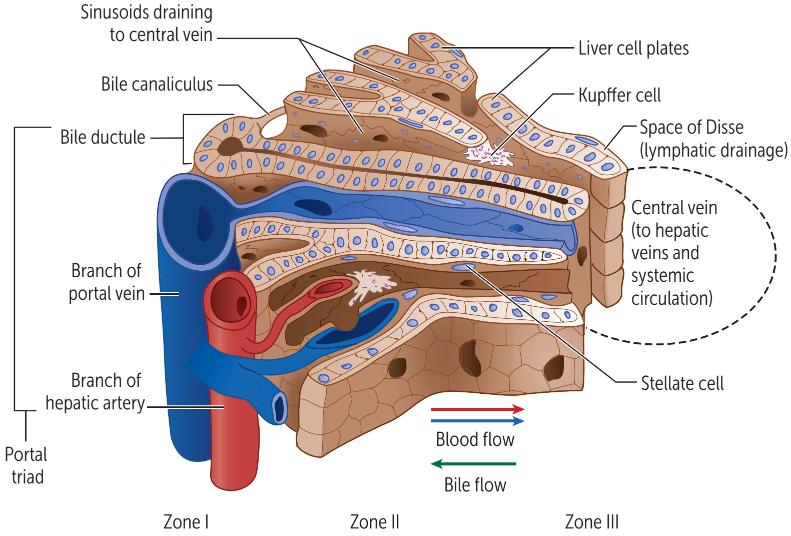
Kupffer cells, which are specialized macrophages, form the lining of these sinusoids (black arrows in A; 2 yellow arrows show hepatic venule).

Hepatic stellate (Ito) cells in space of Disse store vitamin A (when quiescent) and produce extracellular matrix (when activated).

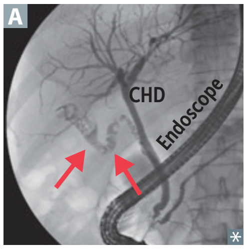
Zone I—periportal zone:
- Affected 1st by viral hepatitis
- Ingested toxins (eg, cocaine)

Zone II—intermediate zone:
- Yellow fever

Zone III—pericentral vein (centrilobular) zone:
- Affected 1st by ischemia
- Contains cytochrome P-450 system
- Most sensitive to metabolic toxins
- Site of alcoholic hepatitis

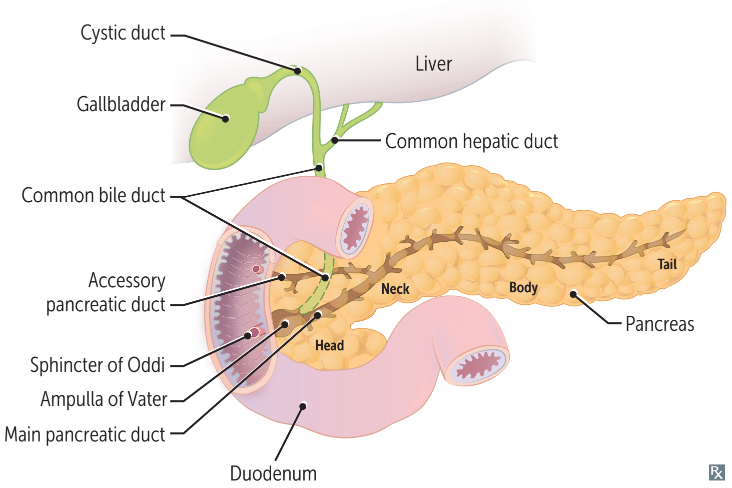

Sinusoids draining to central vein
Bile canaliculus
Bile ductule
Branch of portal vein
Branch of hepatic artery
Portal triad
Liver cell plates
Kupffer cell
Space of Disse (lymphatic drainage)
Central vein (to hepatic veins and systemic circulation)
Stellate cell
Blood flow
Bile flow
Zone I
Zone II
Zone III

Biliary structures


A
CHD
Endoscope

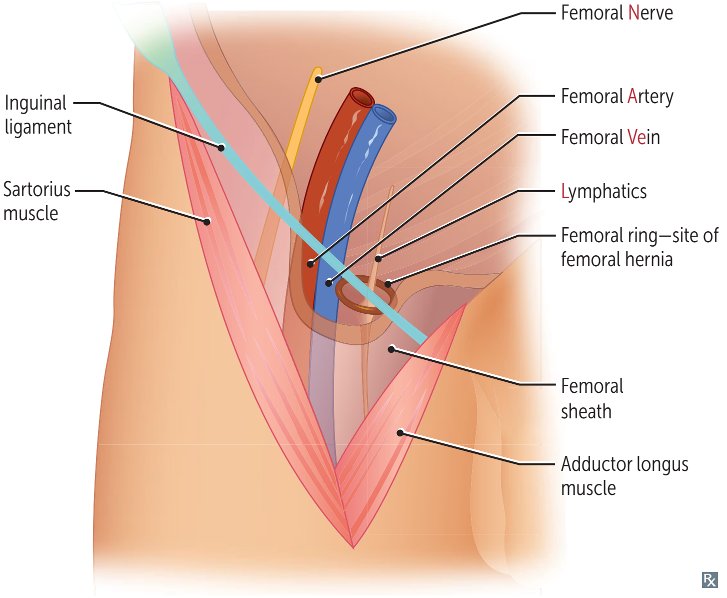
Gallstones (filling defects in gallbladder and cystic duct, red arrows in A) that reach the confluence of the common bile and pancreatic ducts at the ampulla of Vater can block both the common bile and pancreatic ducts (double duct sign), causing both cholangitis and pancreatitis, respectively.

Tumors that arise in head of pancreas (usually ductal adenocarcinoma) can cause obstruction of common bile duct → enlarged gallbladder with painless jaundice (Courvoisier sign).

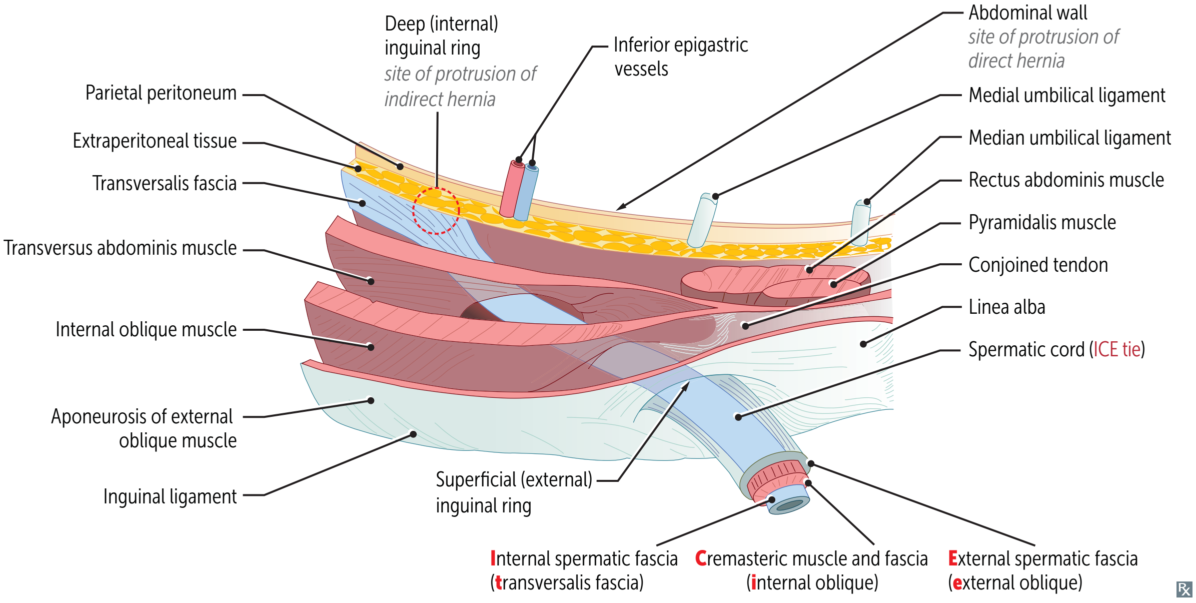

Cystic duct
Liver
Gallbladder
Common hepatic duct
Common bile duct
Accessory pancreatic duct
Neck
Body
Tail
Pancreas
Head
Sphincter of Oddi
Ampulla of Vater
Main pancreatic duct
Duodenum

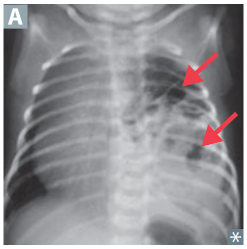
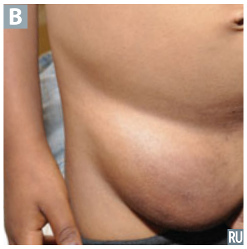
Femoral region

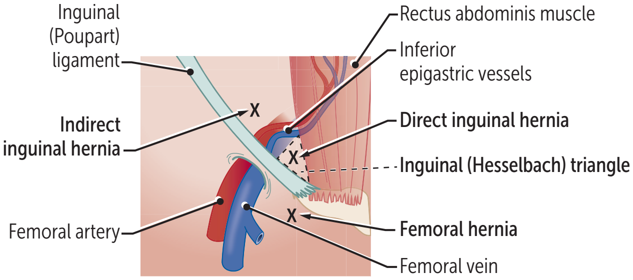
ORGANIZATION	**Lateral to medial**: **N**erve-**A**rtery-**Ve**in-**L**ymphatics.	You go from **lateral to medial** to find your **NAVeL**.
Femoral triangle	Contains femoral nerve, artery, vein.	**Venous** near the **penis**.
Femoral sheath	Fascial tube 3–4 cm below inguinal ligament. Contains femoral vein, artery, and canal (deep inguinal lymph nodes) but not femoral nerve.	


Femoral Nerve
Femoral Artery
Femoral Vein
Lymphatics
Femoral ring—site of femoral hernia
Inguinal ligament
Sartorius muscle
Femoral sheath
Adductor longus muscle

Inguinal canal


Deep (internal) inguinal ring
site of protrusion of indirect hernia
Inferior epigastric vessels
Abdominal wall
site of protrusion of direct hernia
Parietal peritoneum
Medial umbilical ligament
Extraperitoneal tissue
Median umbilical ligament
Transversalis fascia
Rectus abdominis muscle
Pyramidalis muscle
Transversus abdominis muscle
Conjoined tendon
Linea alba
Internal oblique muscle
Spermatic cord (ICE tie)
Aponeurosis of external oblique muscle
Inguinal ligament
Superficial (external) inguinal ring
Internal spermatic fascia (**t**ransversalis fascia)
Cremasteric muscle and fascia (**i**nternal oblique)
External spermatic fascia (**e**xternal oblique)
℞

Hernias	A protrusion of peritoneum through an opening, usually at a site of weakness. Contents may be at risk for incarceration (not reducible back into abdomen/pelvis) and strangulation (ischemia and necrosis). Complicated hernias can present with tenderness, erythema, fever.	
Diaphragmatic hernia  	Abdominal structures enter the thorax A; may occur due to congenital defect of pleuroperitoneal membrane, or as a result of trauma. Commonly occurs on left side due to relative protection of right hemidiaphragm by liver. Most commonly a hiatal hernia, in which stomach herniates upward through the esophageal hiatus of the diaphragm.	Sliding hiatal hernia is most common. Gastroesophageal junction is displaced upward; "hourglass stomach." Paraesophageal hernia—gastroesophageal junction is usually normal. Fundus protrudes into the thorax.
Indirect inguinal hernia  	Goes through the **in**ternal (deep) inguinal ring, external (superficial) inguinal ring, and **in**to the scrotum. Enters internal inguinal ring lateral to inferior epigastric vessels. Occurs in **in**fants owing to failure of processus vaginalis to close (can form hydrocele). Much more common in males B.	An indirect inguinal hernia follows the path of descent of the testes. Covered by all 3 layers of spermatic fascia.
Direct inguinal hernia	Protrudes through the inguinal (Hesselbach) triangle. Bulges directly through parietal peritoneum medial to the inferior epigastric vessels but lateral to the rectus abdominis. Goes through the external (superficial) inguinal ring only. Covered by external spermatic fascia. Usually in older men, due to an acquired weakness in the transversalis fascia.	**MD**s don't **LI**e: **M**edial to inferior epigastric vessels = **D**irect hernia. **L**ateral to inferior epigastric vessels = **I**ndirect hernia.
Femoral hernia	Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle. More common in **fem**ales, but overall inguinal hernias are the most common.	More likely to present with incarceration or strangulation than inguinal hernias.



Inguinal (Hesselbach) triangle:

- Inferior epigastric vessels
- Lateral border of rectus abdominis
- Inguinal ligament

▸ GASTROINTESTINAL—PHYSIOLOGY

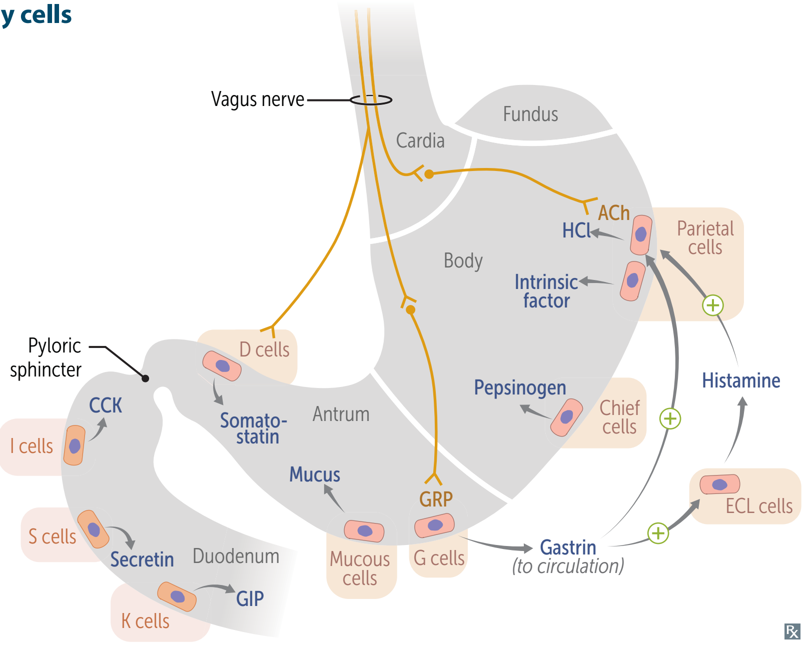
Gastrointestinal regulatory substances

REGULATORY SUBSTANCE	SOURCE	ACTION	REGULATION	NOTES
Gastrin	G cells (antrum of stomach, duodenum)	↑ gastric H$^+$ secretion ↑ growth of gastric mucosa ↑ gastric motility	↑ by stomach distention/alkalinization, amino acids, peptides, vagal stimulation via gastrin-releasing peptide (GRP) ↓ by pH < 1.5	↑ by chronic PPI use. ↑ in chronic atrophic gastritis (eg, *H pylori*). ↑↑ in Zollinger-Ellison syndrome (gastrinoma).
Somatostatin	D cells (pancreatic islets, GI mucosa)	↓ gastric acid and pepsinogen secretion ↓ pancreatic and small intestine fluid secretion ↓ gallbladder contraction ↓ insulin and glucagon release	↑ by acid ↓ by vagal stimulation	Inhibits secretion of various hormones (encourages **somato-sta**sis). Octreotide is an analog used to treat acromegaly, carcinoid syndrome, and variceal bleeding.
Cholecystokinin	I cells (duodenum, jejunum)	↑ pancreatic secretion ↑ gallbladder contraction ↓ gastric emptying ↑ sphincter of Oddi relaxation	↑ by fatty acids, amino acids	Acts on neural muscarinic pathways to cause pancreatic secretion.
Secretin	S cells (duodenum)	↑ pancreatic HCO$_3^-$ secretion ↓ gastric acid secretion ↑ bile secretion	↑ by acid, fatty acids in lumen of duodenum	↑ HCO$_3^-$ neutralizes gastric acid in duodenum, allowing pancreatic enzymes to function.
Glucose-dependent insulinotropic peptide	K cells (duodenum, jejunum)	Exocrine: ↓ gastric H$^+$ secretion Endocrine: ↑ insulin release	↑ by fatty acids, amino acids, oral glucose	Also known as gastric inhibitory peptide (GIP). Oral glucose load leads to ↑ insulin compared to IV equivalent due to GIP secretion.
Motilin	Small intestine	Produces migrating motor complexes (MMCs)	↑ in fasting state	Motilin receptor agonists (eg, erythromycin) are used to stimulate intestinal peristalsis.
Vasoactive intestinal polypeptide	Parasympathetic ganglia in sphincters, gallbladder, small intestine	↑ intestinal water and electrolyte secretion ↑ relaxation of intestinal smooth muscle and sphincters	↑ by distention and vagal stimulation ↓ by adrenergic input	VIPoma—non-α, non-β islet cell pancreatic tumor that secretes VIP. **W**atery **D**iarrhea, **H**ypokalemia, and **A**chlorhydria (**WDHA** syndrome).
Nitric oxide		↑ smooth muscle relaxation, including lower esophageal sphincter (LES)		Loss of NO secretion is implicated in ↑ LES tone of achalasia.
Ghrelin	Stomach	↑ appetite	↑ in fasting state ↓ by food	↑ in Prader-Willi syndrome. ↓ after gastric bypass surgery.

Gastrointestinal secretory products

PRODUCT	SOURCE	ACTION	REGULATION	NOTES
Intrinsic factor	Parietal cells (stomach)	Vitamin B_{12}–binding protein (required for B_{12} uptake in terminal ileum)		Autoimmune destruction of parietal cells → chronic gastritis and pernicious anemia.
Gastric acid	Parietal cells (stomach)	↓ stomach pH	↑ by histamine, ACh, gastrin ↓ by somatostatin, GIP, prostaglandin, secretin	
Pepsin	Chief cells (stomach)	Protein digestion	↑ by vagal stimulation, local acid	Pepsinogen (inactive) is converted to pepsin (active) in the presence of H^+.
Bicarbonate	Mucosal cells (stomach, duodenum, salivary glands, pancreas) and Brunner glands (duodenum)	Neutralizes acid	↑ by pancreatic and biliary secretion with secretin	Trapped in mucus that covers the gastric epithelium.

Locations of gastrointestinal secretory cells


Vagus nerve
Fundus
Cardia
ACh
HCl
Parietal cells
Body
Intrinsic factor
Pyloric sphincter
D cells
Somatostatin
Antrum
Pepsinogen
Chief cells
Histamine
CCK
I cells
Mucus
GRP
S cells
Secretin
Duodenum
Mucous cells
G cells
Gastrin
(to circulation)
ECL cells
GIP
K cells
+

Gastrin ↑ acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells.

Pancreatic secretions

Isotonic fluid; low flow → high Cl^-, high flow → high HCO_3^-.

ENZYME	ROLE	NOTES
α-amylase	Starch digestion	Secreted in active form
Lipases	Fat digestion	
Proteases	Protein digestion	Includes trypsin, chymotrypsin, elastase, carboxypeptidases Secreted as proenzymes also known as zymogens
Trypsinogen	Converted to active enzyme trypsin → activation of other proenzymes and cleaving of additional trypsinogen molecules into active trypsin (positive feedback loop)	Converted to trypsin by enterokinase/enteropeptidase, a brush-border enzyme on duodenal and jejunal mucosa

Carbohydrate absorption

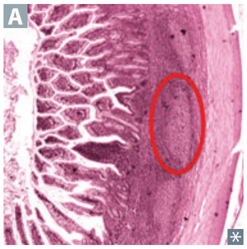
Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes. Glucose and galactose are taken up by SGLT1 (Na^+ dependent). Fructose is taken up by facilitated diffusion by GLUT5. All are transported to blood by GLUT2.

D-xylose absorption test: distinguishes GI mucosal damage from other causes of malabsorption.

Vitamin/mineral absorption

Iron	Absorbed as Fe^{2+} in duodenum.	**I**ron **F**ist, **B**ro
Folate	Absorbed in small bowel.	Clinically relevant in patients with small bowel disease or after resection.
B_{12}	Absorbed in terminal ileum along with bile salts, requires intrinsic factor.	

Peyer patches



Unencapsulated lymphoid tissue A found in lamina propria and submucosa of ileum. Contain specialized M cells that sample and present antigens to immune cells.

B cells stimulated in germinal centers of Peyer patches differentiate into IgA-secreting plasma cells, which ultimately reside in lamina propria. IgA receives protective secretory component and is then transported across the epithelium to the gut to deal with intraluminal antigen.

Think of **IgA**, the **I**ntra-**g**ut **A**ntibody. And always say "secretory IgA."

Bile

Composed of bile salts (bile acids conjugated to glycine or taurine, making them water soluble), phospholipids, cholesterol, bilirubin, water, and ions. Cholesterol 7α-hydroxylase catalyzes rate-limiting step of bile acid synthesis.

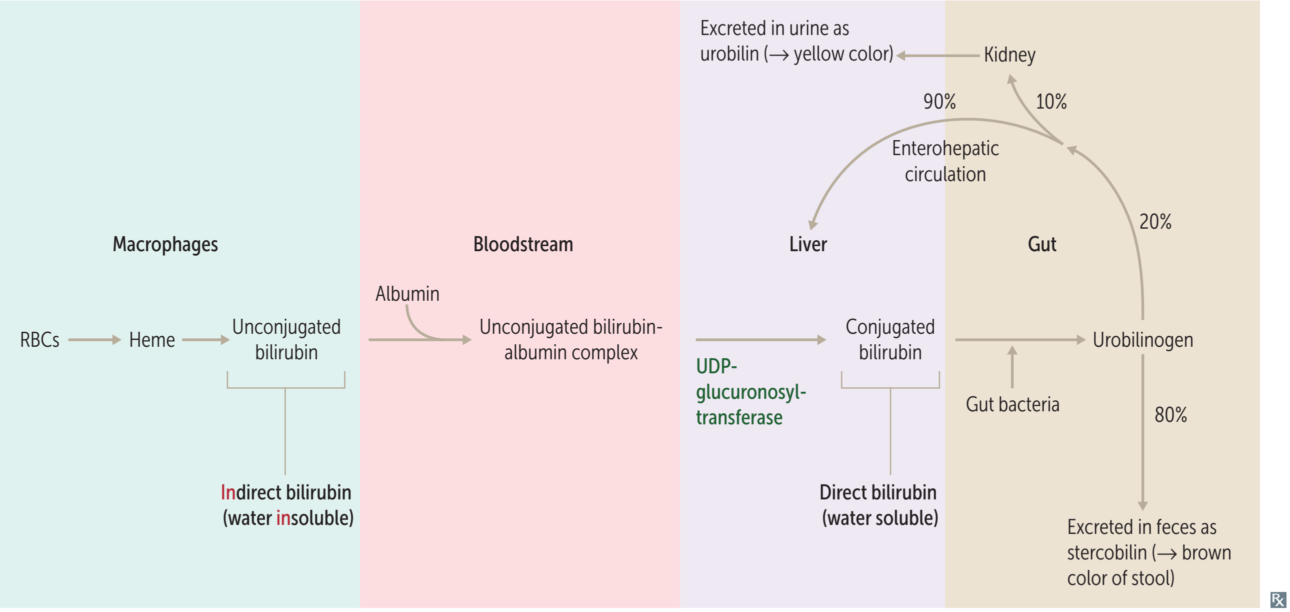
Functions:
- Digestion and absorption of lipids and fat-soluble vitamins
- Cholesterol excretion (body's 1° means of eliminating cholesterol)
- Antimicrobial activity (via membrane disruption)

Bilirubin

Heme is metabolized by heme oxygenase to biliverdin, which is subsequently reduced to bilirubin. Unconjugated bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile.

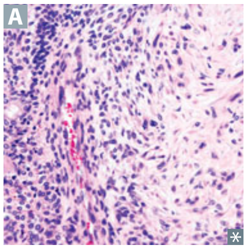
Direct bilirubin—conjugated with glucuronic acid; water soluble.

Indirect bilirubin—unconjugated; water insoluble.


Macrophages
Bloodstream
Liver
Gut
RBCs
Heme
Unconjugated bilirubin
Indirect bilirubin (water insoluble)
Albumin
Unconjugated bilirubin-albumin complex
UDP-glucuronosyl-transferase
Conjugated bilirubin
Direct bilirubin (water soluble)
Gut bacteria
Urobilinogen
80%
Excreted in feces as stercobilin (→ brown color of stool)
20%
Enterohepatic circulation
90%
10%
Kidney
Excreted in urine as urobilin (→ yellow color)

▶ GASTROINTESTINAL—PATHOLOGY

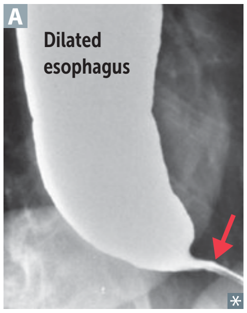
Salivary gland tumors



Most commonly benign and in parotid gland. Tumors in smaller glands more likely malignant. Typically present as painless mass/swelling. Facial pain or paralysis suggests malignant involvement of CN VII.

- Pleomorphic adenoma (benign mixed tumor)—most common salivary gland tumor A. Composed of chondromyxoid stroma and epithelium and recurs if incompletely excised or ruptured intraoperatively.
- Mucoepidermoid carcinoma—most common malignant tumor, has mucinous and squamous components.
- Warthin tumor (papillary cystadenoma lymphomatosum)—benign cystic tumor with germinal centers. Typically found in smokers. Bilateral in 10%; malignant in 10%.

Achalasia

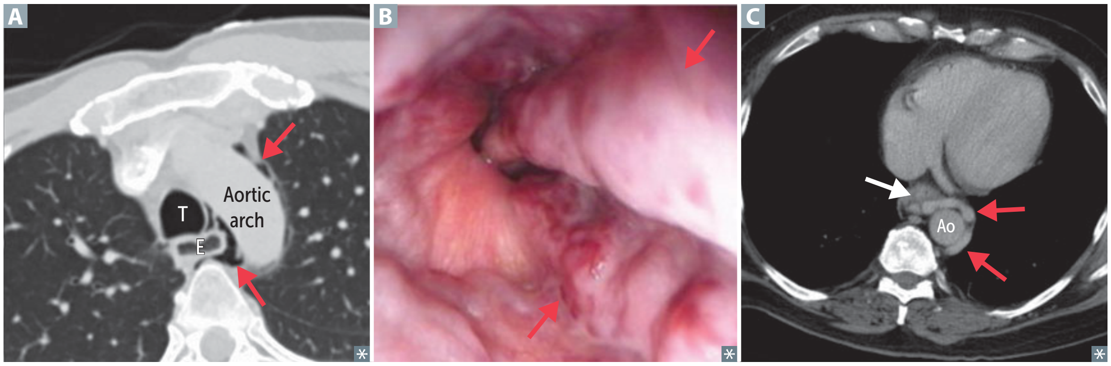


Failure of LES to relax due to loss of myenteric (Auerbach) plexus → loss of postganglionic inhibitory neurons (that contain NO and VIP). High LES resting pressure and uncoordinated or absent peristalsis → progressive dysphagia to solids and liquids (vs obstruction—solids only). Barium swallow shows dilated esophagus with an area of distal stenosis. Associated with ↑ risk of esophageal cancer.

A-*chalasia* = absence of relaxation.
"Bird's beak" on barium swallow A.
2° achalasia may arise from Chagas disease (*T cruzi* infection) or extraesophageal malignancies (mass effect or paraneoplastic).

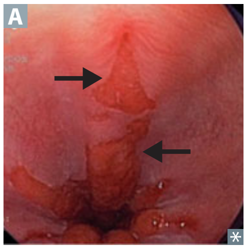
Esophageal pathologies

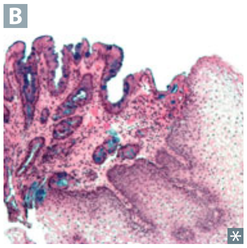
Boerhaave syndrome	Transmural, usually distal esophageal rupture with pneumomediastinum (arrows in A) due to violent retching. Subcutaneous emphysema may be due to dissecting air (crepitus may be felt in the neck region or chest wall). Surgical emergency.
Eosinophilic esophagitis	Infiltration of eosinophils in the esophagus often in atopic patients. Food allergens → dysphagia, food impaction. Esophageal rings and linear furrows often seen on endoscopy. Unresponsive to GERD therapy.
Esophageal strictures	Associated with caustic ingestion and acid reflux.
Esophageal varices	Dilated submucosal veins (red arrows) B C in lower ⅓ of esophagus (white arrow) 2° to portal hypertension. Common in cirrhotics, may be source of life-threatening hematemesis.
Esophagitis	Associated with reflux, infection in immunocompromised (*Candida*: white pseudomembrane; HSV-1: punched-out ulcers; CMV: linear ulcers), caustic ingestion, or pill esophagitis (eg, bisphosphonates, tetracycline, NSAIDs, iron, and potassium chloride).
Gastroesophageal reflux disease	Commonly presents as heartburn, regurgitation, dysphagia. May also present as chronic cough, hoarseness (laryngopharyngeal reflux). Associated with asthma. Transient decreases in LES tone.
Mallory-Weiss syndrome	Partial-thickness mucosal lacerations at gastroesophageal junction due to severe vomiting. Often presents with hematemesis and may be misdiagnosed as ruptured esophageal varices. Usually found in alcoholics and bulimics.
Plummer-Vinson syndrome	Triad of **D**ysphagia, **I**ron deficiency anemia, and **E**sophageal webs. May be associated with glossitis. Increased risk of esophageal squamous cell carcinoma ("**Plumbers**" **DIE**).
Sclerodermal esophageal dysmotility	Esophageal smooth muscle atrophy → ↓ LES pressure and dysmotility → acid reflux and dysphagia → stricture, Barrett esophagus, and aspiration. Part of CREST syndrome.

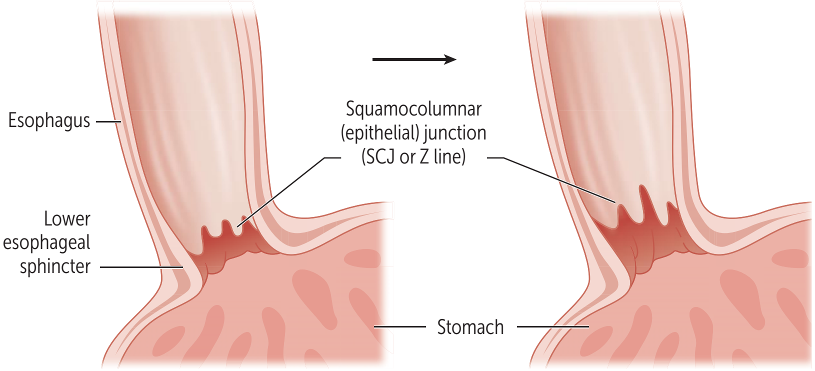


Barrett esophagus

Specialized intestinal metaplasia A—replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells [stained blue in B]) in distal esophagus. Due to chronic gastroesophageal reflux (GERD). Associated with ↑ risk of esophageal adenocarcinoma.






Esophagus
Lower esophageal sphincter
Squamocolumnar (epithelial) junction (SCJ or Z line)
Stomach

Esophageal cancer

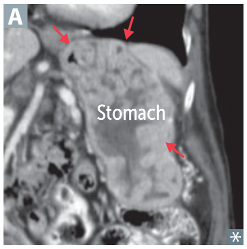
Typically presents with progressive dysphagia (first solids, then liquids) and weight loss; poor prognosis.

CANCER	PART OF ESOPHAGUS AFFECTED	RISK FACTORS	PREVALENCE
Squamous cell carcinoma	Upper 2/3	Alcohol, hot liquids, caustic strictures, smoking, achalasia	More common worldwide
Adenocarcinoma	Lower 1/3	Chronic GERD, Barrett esophagus, obesity, smoking, achalasia	More common in America

Gastritis

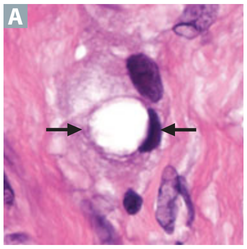
Acute gastritis	Erosions can be caused by: ▪ NSAIDs—↓ PGE$_2$ → ↓ gastric mucosa protection ▪ Burns (Curling ulcer)—hypovolemia → mucosal ischemia ▪ Brain injury (Cushing ulcer)—↑ vagal stimulation → ↑ ACh → ↑ H$^+$ production	Especially common among alcoholics and patients taking daily NSAIDs (eg, patients with rheumatoid arthritis). **Burn**ed by the **Curling** iron. Always **Cush**ion the **brain**.
Chronic gastritis	Mucosal inflammation, often leading to atrophy (hypochlorhydria → hypergastrinemia) and intestinal G-cell metaplasia (↑ risk of gastric cancers).	
H pylori	Most common. ↑ risk of peptic ulcer disease, MALT lymphoma.	Affects antrum first and spreads to body of stomach.
Autoimmune	Autoantibodies to parietal cells and intrinsic factor. ↑ risk of pernicious anemia.	Affects body/fundus of stomach.

Ménétrier disease



Hyperplasia of gastric mucosa → hypertrophied rugae (look like brain gyri A), excess mucus production with resultant protein loss and parietal cell atrophy with ↓ acid production. Precancerous.

Gastric cancer



Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoid (rare). Early aggressive local spread with node/liver metastases. Often presents late, with weight loss, early satiety, and in some cases acanthosis nigricans or Leser-Trélat sign.

- **Intestinal**—associated with *H pylori*, dietary nitrosamines (smoked foods), tobacco smoking, achlorhydria, chronic gastritis. Commonly on lesser curvature; looks like ulcer with raised margins.
- **Diffuse**—not associated with *H pylori*; signet ring cells (mucin-filled cells with peripheral nuclei) A; stomach wall grossly thickened and leathery (linitis plastica).

Virchow node—involvement of left supraclavicular node by metastasis from stomach.

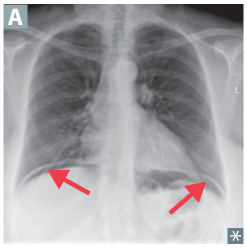
Krukenberg tumor—bilateral metastases to ovaries. Abundant mucin-secreting, signet ring cells.

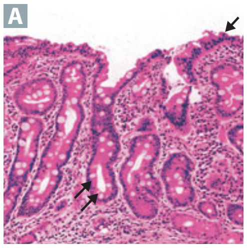
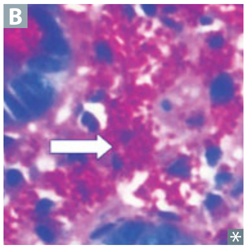
Sister Mary Joseph nodule—subcutaneous periumbilical metastasis.

Peptic ulcer disease

	Gastric ulcer	Duodenal ulcer
PAIN	Can be Greater with meals—weight loss	Decreases with meals—weight gain
H PYLORI INFECTION	~ 70%	~ 90%
MECHANISM	↓ mucosal protection against gastric acid	↓ mucosal protection or ↑ gastric acid secretion
OTHER CAUSES	NSAIDs	Zollinger-Ellison syndrome
RISK OF CARCINOMA	↑	Generally benign
OTHER	Biopsy margins to rule out malignancy	Hypertrophy of Brunner glands

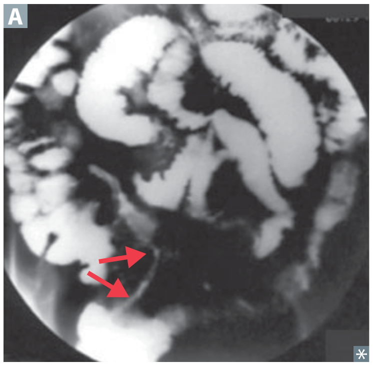
Ulcer complications

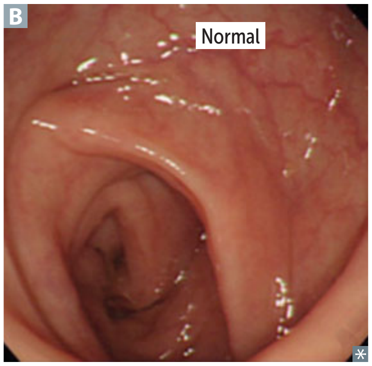
Hemorrhage	Gastric, duodenal (posterior > anterior). Most common complication. Ruptured gastric ulcer on the lesser curvature of stomach → bleeding from left gastric artery. An ulcer on the posterior wall of duodenum → bleeding from gastroduodenal artery.
Obstruction	Pyloric channel, duodenal
Perforation 	Duodenal (anterior > posterior). May see free air under diaphragm A with referred pain to the shoulder via irritation of phrenic nerve.

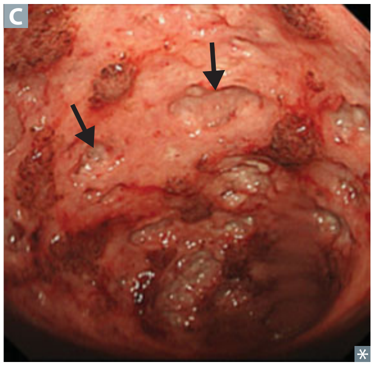
Malabsorption syndromes	Can cause diarrhea, steatorrhea, weight loss, weakness, vitamin and mineral deficiencies. Screen for fecal fat (eg, Sudan stain).	
Celiac disease 	Gluten-sensitive enteropathy, celiac sprue. Autoimmune-mediated intolerance of gliadin (gluten protein found in wheat) → malabsorption and steatorrhea. Associated with HLA-DQ2, HLA-DQ8, northern European descent, dermatitis herpetiformis, ↓ bone density. Findings: IgA anti-tissue transglutaminase (IgA tTG), anti-endomysial, anti-deamidated gliadin peptide antibodies; villous atrophy (arrow in A shows blunting), crypt hyperplasia (double arrows in A), and intraepithelial lymphocytosis. Moderately ↑ risk of malignancy (eg, T-cell lymphoma).	↓ mucosal absorption primarily affects distal duodenum and/or proximal jejunum. D-xylose test: passively absorbed in proximal small intestine; blood and urine levels ↓ with mucosa defects or bacterial overgrowth, normal in pancreatic insufficiency. Treatment: gluten-free diet.
Lactose intolerance	Lactase deficiency. Normal-appearing villi, except when 2° to injury at tips of villi (eg, viral enteritis). Osmotic diarrhea with ↓ stool pH (colonic bacteria ferment lactose).	Lactose hydrogen breath test: ⊕ for lactose malabsorption if postlactose breath hydrogen value rises > 20 ppm compared with baseline.
Pancreatic insufficiency	Due to chronic pancreatitis, cystic fibrosis, obstructing cancer. Causes malabsorption of fat and fat-soluble vitamins (A, D, E, K) as well as vitamin B_{12}.	↓ duodenal pH (bicarbonate) and fecal elastase.
Tropical sprue	Similar findings as celiac sprue (affects small bowel), but responds to antibiotics. Cause is unknown, but seen in residents of or recent visitors to tropics.	↓ mucosal absorption affecting duodenum and jejunum but can involve ileum with time. Associated with megaloblastic anemia due to folate deficiency and, later, B_{12} deficiency.
Whipple disease 	Infection with *Tropheryma whipplei* (intracellular gram ⊕); PAS ⊕ **foamy** macrophages in intestinal lamina propria B, mesenteric nodes. **C**ardiac symptoms, **A**rthralgias, and **N**eurologic symptoms are common. Diarrhea/steatorrhea occur later in disease course. Most common in older men.	**Foamy Whipp**ed cream in a **CAN**.

Inflammatory bowel disease

	Crohn disease	Ulcerative colitis
LOCATION	Any portion of the GI tract, usually the terminal ileum and colon. **Skip** lesions, **rec**tal sparing.	Colitis = colon inflammation. Continuous colonic lesions, always with rectal involvement.
GROSS MORPHOLOGY	Transmural inflammation → fistulas. **Cobblestone** mucosa, creeping **fat**, bowel wall thickening ("string sign" on barium swallow x-ray A), linear ulcers, fissures.	Mucosal and submucosal inflammation only. Friable mucosa with superficial and/or deep ulcerations (compare normal B with diseased C). Loss of haustra → "lead pipe" appearance on imaging.
MICROSCOPIC MORPHOLOGY	Noncaseating **gran**ulomas and lymphoid aggregates. Th1 mediated.	Crypt abscesses and ulcers, bleeding, no granulomas. Th2 mediated.
COMPLICATIONS	Malabsorption/malnutrition, colorectal cancer (↑ risk with pancolitis).	
	Fistulas (eg, enterovesical fistulae, which can cause recurrent UTI and pneumaturia), phlegmon/abscess, strictures (causing obstruction), perianal disease.	Fulminant colitis, toxic megacolon, perforation.
INTESTINAL MANIFESTATION	Diarrhea that may or may not be bloody.	Bloody diarrhea.
EXTRAINTESTINAL MANIFESTATIONS	Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis).	
	Kidney stones (usually calcium oxalate), gallstones. May be ⊕ for anti-*Saccharomyces cervisiae* antibodies (ASCA).	1° sclerosing cholangitis. Associated with p-ANCA.
TREATMENT	Corticosteroids, azathioprine, antibiotics (eg, ciprofloxacin, metronidazole), infliximab, adalimumab.	5-aminosalicylic preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy.
	For **Crohn**, think of a **fat gran**ny and an old **crone skip**ping down a **cobblestone** road away from the **wreck** (rectal sparing).	Ulcerative colitis causes **ULCCCERS**: **U**lcers **L**arge intestine **C**ontinuous, **C**olorectal carcinoma, **C**rypt abscesses **E**xtends proximally **R**ed diarrhea **S**clerosing cholangitis







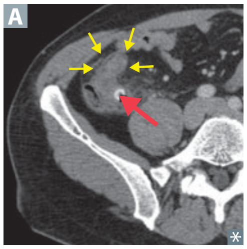
Irritable bowel syndrome

Recurrent abdominal pain associated with ≥ 2 of the following:

- Related to defecation
- Change in stool frequency
- Change in form (consistency) of stool

No structural abnormalities. Most common in middle-aged women. Chronic symptoms may be diarrhea-predominant, constipation-predominant, or mixed. Pathophysiology is multifaceted.

Appendicitis



Acute inflammation of the appendix (yellow arrows in A), can be due to obstruction by fecalith (red arrow in A) (in adults) or lymphoid hyperplasia (in children).

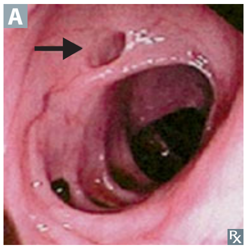
Initial diffuse periumbilical pain migrates to McBurney point (⅓ the distance from right anterior superior iliac spine to umbilicus). Nausea, fever; may perforate → peritonitis; may elicit psoas, obturator, and Rovsing signs, guarding and rebound tenderness on exam.

Differential: diverticulitis (elderly), ectopic pregnancy (use β-hCG to rule out).

Treatment: appendectomy.

Diverticula of the GI tract

Diverticulum



Blind pouch A protruding from the alimentary tract that communicates with the lumen of the gut. Most diverticula (esophagus, stomach, duodenum, colon) are acquired and are termed "false diverticula."

"True" diverticulum—all 3 gut wall layers outpouch (eg, Meckel).

"False" diverticulum or pseudodiverticulum—only mucosa and submucosa outpouch. Occur especially where vasa recta perforate muscularis externa.

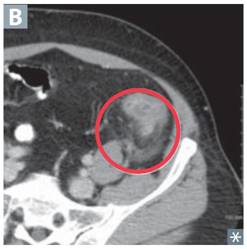
Diverticulosis

Many false diverticula of the colon, commonly sigmoid. Common (in ~ 50% of people > 60 years). Caused by ↑ intraluminal pressure and focal weakness in colonic wall. Associated with low-fiber diets.

Often asymptomatic or associated with vague discomfort.

Complications include diverticular bleeding (painless hematochezia), diverticulitis.

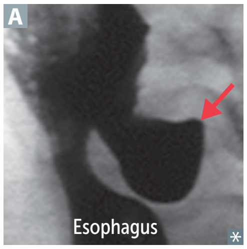
Diverticulitis



Inflammation of diverticula B classically causing LLQ pain, fever, leukocytosis. Treat with antibiotics.

Complications: abscess, fistula (colovesical fistula → pneumaturia), obstruction (inflammatory stenosis), perforation (→ peritonitis).

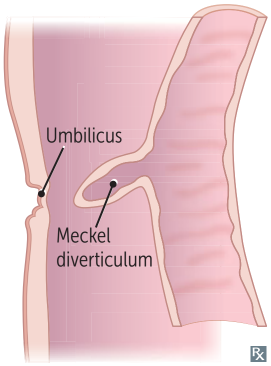
Zenker diverticulum



Pharyngoesophageal **false** diverticulum A. Esophageal dysmotility causes herniation of mucosal tissue at Killian triangle between the thyropharyngeal and cricopharyngeal parts of the inferior pharyngeal constrictor. Presenting symptoms: dysphagia, obstruction, gurgling, aspiration, foul breath, neck mass. Most common in elderly males.

Elder MIKE has bad breath.
Elderly
Males
Inferior pharyngeal constrictor
Killian triangle
Esophageal dysmotility
Halitosis

Meckel diverticulum

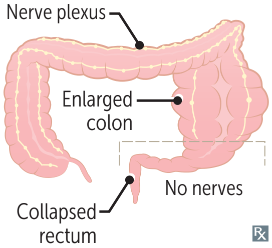


True diverticulum. Persistence of the vitelline duct. May contain ectopic acid–secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of GI tract. Can cause hematochezia/melena (less commonly), RLQ pain, intussusception, volvulus, or obstruction near terminal ileum. Contrast with omphalomesenteric cyst = cystic dilation of vitelline duct.

Diagnosis: pertechnetate study for uptake by ectopic gastric mucosa.

The rule of 2's:
- 2 times as likely in males.
- 2 inches long.
- 2 feet from the ileocecal valve.
- 2% of population.
- Commonly presents in first 2 years of life.
- May have 2 types of epithelia (gastric/pancreatic).

Hirschsprung disease



Congenital megacolon characterized by lack of ganglion cells/enteric nervous plexuses (Auerbach and Meissner plexuses) in distal segment of colon. Due to failure of neural crest cell migration. Associated with mutations in *RET*.

Presents with bilious emesis, abdominal distention, and failure to pass meconium within 48 hours → chronic constipation. Normal portion of the colon proximal to the aganglionic segment is dilated, resulting in a "transition zone."

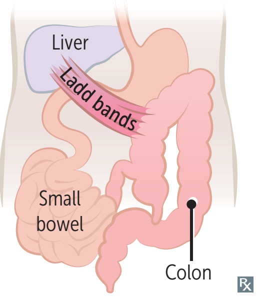
Risk ↑ with Down syndrome.

Explosive expulsion of feces (squirt sign) → empty rectum on digital exam.

Diagnosed by absence of ganglionic cells on rectal suction biopsy.

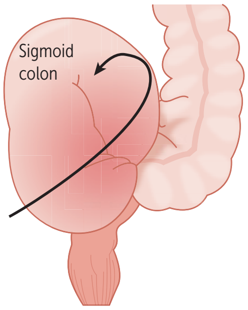
Treatment: resection.

Malrotation

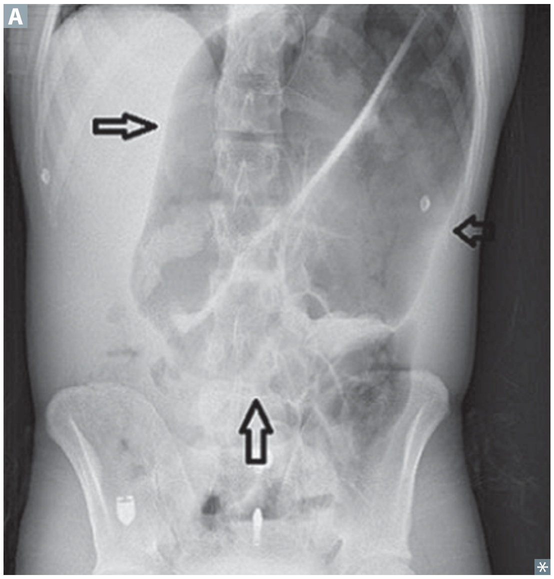


Anomaly of midgut rotation during fetal development → improper positioning of bowel, formation of fibrous bands (Ladd bands). Can lead to volvulus, duodenal obstruction.

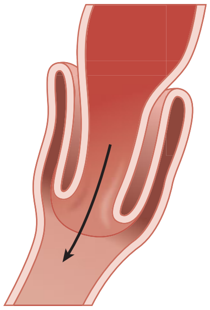
Volvulus



Twisting of portion of bowel around its mesentery; can lead to obstruction and infarction. Can occur throughout the GI tract. Midgut volvulus more common in infants and children. Sigmoid volvulus (coffee bean sign on x-ray **A**) more common in elderly.

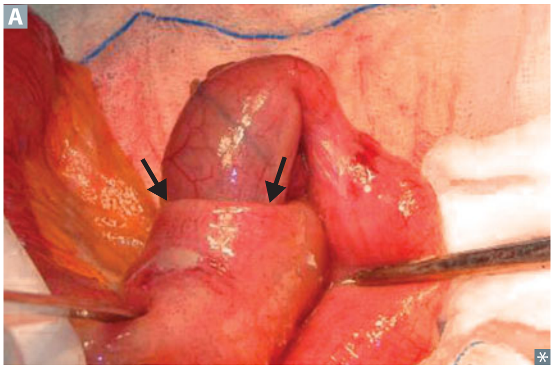


Intussusception



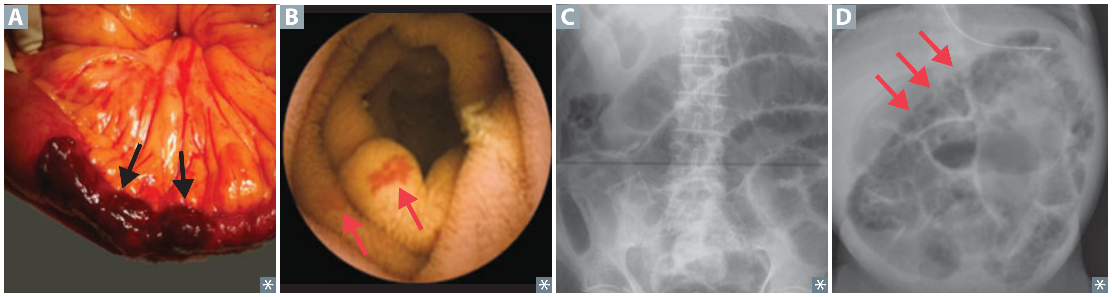
Telescoping **A** of proximal bowel segment into distal segment, commonly at ileocecal junction. Compromised blood supply → intermittent abdominal pain often with "currant jelly" stools. Unusual in adults (associated with intraluminal mass or tumor that acts as lead point that is pulled into the lumen). Most common pathologic lead point is Meckel diverticulum.

Majority of cases occur in children and are idiopathic. May be associated with recent viral infection, such as adenovirus → Peyer patch hypertrophy → lead point. Also associated with rotavirus vaccine.

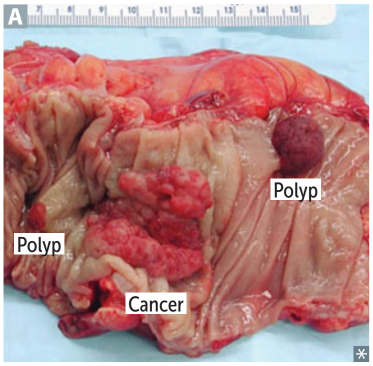


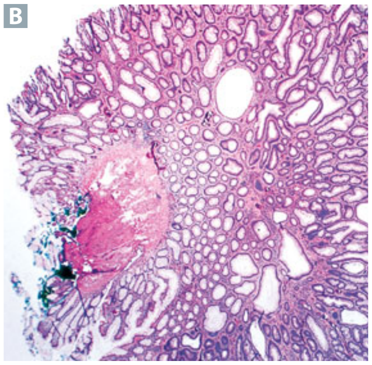
Other intestinal disorders

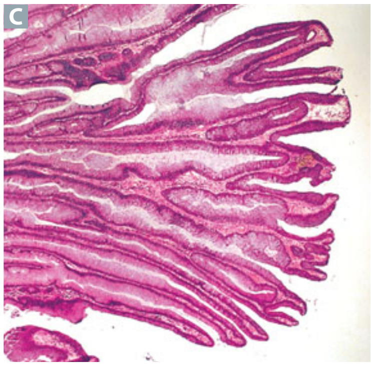
Acute mesenteric ischemia	Critical blockage of intestinal blood flow (often embolic occlusion of SMA) → small bowel necrosis A → abdominal pain out of proportion to physical findings. May see red "currant jelly" stools.
Chronic mesenteric ischemia	"Intestinal angina": atherosclerosis of celiac artery, SMA, or IMA → intestinal hypoperfusion → postprandial epigastric pain → food aversion and weight loss.
Colonic ischemia	Reduction in intestinal blood flow causes ischemia. Crampy abdominal pain followed by hematochezia. Commonly occurs at watershed areas (splenic flexure, distal colon). Typically affects elderly. Thumbprint sign on imaging due to mucosal edema/hemorrhage.
Angiodysplasia	Tortuous dilation of vessels B → hematochezia. Most often found in the right-sided colon. More common in older patients. Confirmed by angiography.
Adhesion	Fibrous band of scar tissue; commonly forms after surgery; most common cause of small bowel obstruction C. Can have well-demarcated necrotic zones.
Ileus	Intestinal hypomotility without obstruction → constipation and ↓ flatus; distended/tympanic abdomen with ↓ bowel sounds. Associated with abdominal surgeries, opiates, hypokalemia, sepsis. Treatment: bowel rest, electrolyte correction, cholinergic drugs (stimulate intestinal motility).
Meconium ileus	In cystic fibrosis, meconium plug obstructs intestine, preventing stool passage at birth.
Necrotizing enterocolitis	Seen in premature, formula-fed infants with immature immune system. Necrosis of intestinal mucosa (primarily colonic) with possible perforation, which can lead to pneumatosis intestinalis D, free air in abdomen, portal venous gas.



Colonic polyps	Growths of tissue within the colon A. May be neoplastic or non-neoplastic. Grossly characterized as flat, sessile, or pedunculated (on a stalk) on the basis of protrusion into colonic lumen. Generally classified by histologic type.
HISTOLOGIC TYPE	CHARACTERISTICS
Generally non-neoplastic	
Hamartomatous polyps	Solitary lesions do not have significant risk of transformation. Growths of normal colonic tissue with distorted architecture. Associated with Peutz-Jeghers syndrome and juvenile polyposis.
Mucosal polyps	Small, usually < 5 mm. Look similar to normal mucosa. Clinically insignificant.
Inflammatory pseudopolyps	Result of mucosal erosion in inflammatory bowel disease.
Submucosal polyps	May include lesions such as lipomas, leiomyomas, fibromas, and others.
Hyperplastic polyps	Generally smaller and predominantly located in the rectosigmoid region. May occasionally evolve into serrated polyps and more advanced lesions.
Malignant potential	
Adenomatous polyps	Neoplastic, via chromosomal instability pathway with mutations in *APC* and *KRAS*. Tubular B histology has less malignant potential than villous C ("VILLOUS histology is VILLainOUS"); tubulovillous has intermediate malignant potential. Usually asymptomatic; may present with occult bleeding.
Serrated polyps	Premalignant, via CpG hypermethylation phenotype pathway with microsatellite instability and mutations in *BRAF*. "Saw-tooth" pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC.



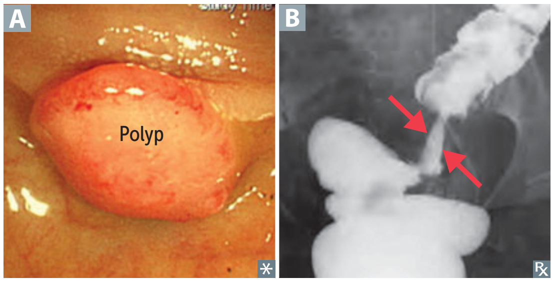




Polyposis syndromes	
Familial adenomatous polyposis	Autosomal dominant mutation of *APC* tumor suppressor gene on chromosome 5q. 2-hit hypothesis. Thousands of polyps arise starting after puberty; pancolonic; always involves rectum. Prophylactic colectomy or else 100% progress to CRC.
Gardner syndrome	FAP + osseous and soft tissue tumors, congenital hypertrophy of retinal pigment epithelium, impacted/supernumerary teeth.
Turcot syndrome	FAP/Lynch syndrome + malignant CNS tumor (eg, medulloblastoma, glioma). Turcot = Turban.
Peutz-Jeghers syndrome	Autosomal dominant syndrome featuring numerous hamartomas throughout GI tract, along with hyperpigmented mouth, lips, hands, genitalia. Associated with ↑ risk of breast and GI cancers (eg, colorectal, stomach, small bowel, pancreatic).
Juvenile polyposis syndrome	Autosomal dominant syndrome in children (typically < 5 years old) featuring numerous hamartomatous polyps in the colon, stomach, small bowel. Associated with ↑ risk of CRC.

Lynch syndrome	Previously known as hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant mutation of DNA mismatch repair genes with subsequent microsatellite instability. ~ 80% progress to CRC. Proximal colon is always involved. Associated with endometrial, ovarian, and skin cancers.

Colorectal cancer

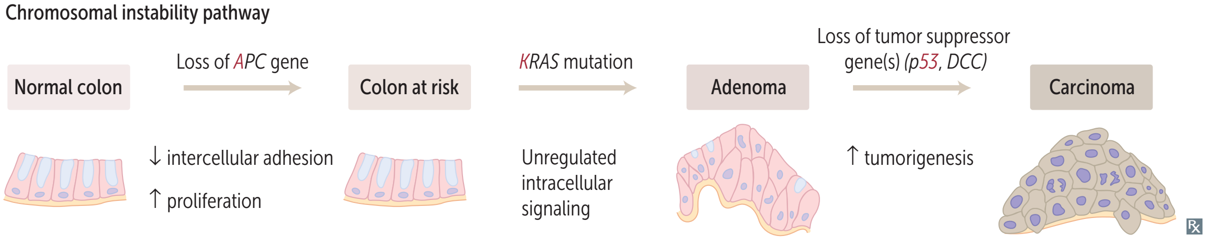
EPIDEMIOLOGY	Most patients are > 50 years old. ~ 25% have a family history.	
RISK FACTORS	Adenomatous and serrated polyps, familial cancer syndromes, IBD, tobacco use, diet of processed meat with low fiber.	
PRESENTATION	Rectosigmoid > ascending > descending. Ascending—exophytic mass, iron deficiency anemia, weight loss. Descending—infiltrating mass, partial obstruction, colicky pain, hematochezia. Rarely, presents with *S bovis (gallolyticus)* bacteremia.	Right side bleeds; left side obstructs.
DIAGNOSIS	Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion. Screen low-risk patients starting at age 50 with colonoscopy A; alternatives include flexible sigmoidoscopy, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), and CT colonography. Patients with a first-degree relative who has colon cancer should be screened via colonoscopy at age 40, or starting 10 years prior to their relative's presentation. Patients with IBD have a distinct screening protocol. "Apple core" lesion seen on barium enema x-ray B. CEA tumor marker: good for monitoring recurrence, should not be used for screening.	

Molecular pathogenesis of colorectal cancer

Chromosomal instability pathway: mutations in *APC* cause FAP and most sporadic CRC (via adenoma-carcinoma sequence; (**firing**) order of events is **AK-53**).

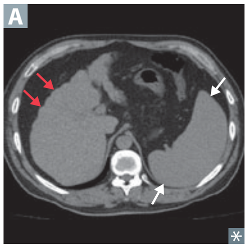
Microsatellite instability pathway: mutations or methylation of mismatch repair genes (eg, *MLH1*) cause Lynch syndrome and some sporadic CRC (via serrated polyp pathway).

Overexpression of COX-2 has been linked to colorectal cancer, NSAIDs may be chemopreventive.


Chromosomal instability pathway

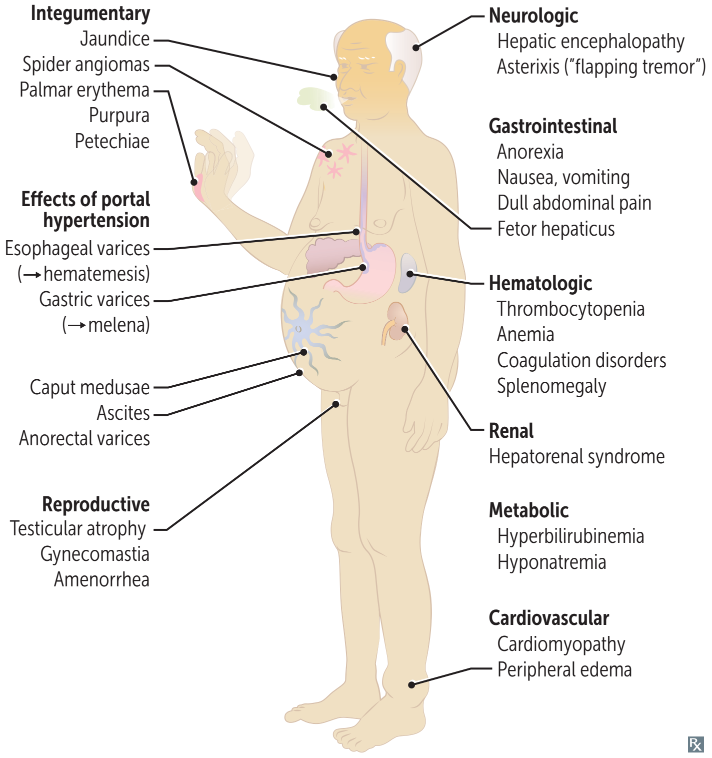
Normal colon
Loss of *APC* gene
Colon at risk
KRAS mutation
Adenoma
Loss of tumor suppressor gene(s) (*p53*, *DCC*)
Carcinoma
↓ intercellular adhesion
↑ proliferation
Unregulated intracellular signaling
↑ tumorigenesis

Cirrhosis and portal hypertension



Cirrhosis—diffuse bridging fibrosis (via stellate cells) and regenerative nodules (red arrows in A; white arrows shows splenomegaly) disrupt normal architecture of liver; ↑ risk for hepatocellular carcinoma (HCC). Etiologies include alcohol (60–70% of cases in the US), nonalcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, biliary disease, genetic/metabolic disorders.

Portal hypertension—↑ pressure in portal venous system. Etiologies include cirrhosis (most common cause in Western countries), vascular obstruction (eg, portal vein thrombosis, Budd-Chiari syndrome), schistosomiasis.



Integumentary
Jaundice
Spider angiomas
Palmar erythema
Purpura
Petechiae
Effects of portal hypertension
Esophageal varices
(→hematemesis)
Gastric varices
(→melena)
Caput medusae
Ascites
Anorectal varices
Reproductive
Testicular atrophy
Gynecomastia
Amenorrhea
Neurologic
Hepatic encephalopathy
Asterixis ("flapping tremor")
Gastrointestinal
Anorexia
Nausea, vomiting
Dull abdominal pain
Fetor hepaticus
Hematologic
Thrombocytopenia
Anemia
Coagulation disorders
Splenomegaly
Renal
Hepatorenal syndrome
Metabolic
Hyperbilirubinemia
Hyponatremia
Cardiovascular
Cardiomyopathy
Peripheral edema

Spontaneous bacterial peritonitis	Also known as 1° bacterial peritonitis. Common and potentially fatal bacterial infection in patients with cirrhosis and ascites. Often asymptomatic, but can cause fevers, chills, abdominal pain, ileus, or worsening encephalopathy. Commonly caused by aerobic gram ⊖ organisms, especially *E coli*. Diagnosis: Paracentesis with ascitic fluid absolute neutrophil count (ANC) > 250 cells/mm^3.

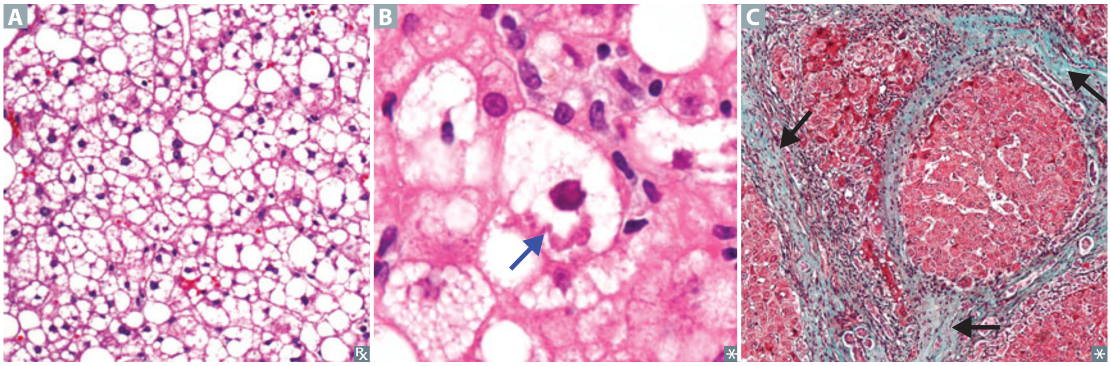
Serum markers of liver pathology

ENZYMES RELEASED IN LIVER DAMAGE	
Aspartate aminotransferase and alanine aminotransferase	↑ in most liver disease: ALT > AST ↑ in alcoholic liver disease: AST > ALT AST > ALT in nonalcoholic liver disease suggests progression to advanced fibrosis or cirrhosis
Alkaline phosphatase	↑ in cholestasis (eg, biliary obstruction), infiltrative disorders, bone disease
γ-glutamyl transpeptidase	↑ in various liver and biliary diseases (just as ALP can), but not in bone disease; associated with alcohol use
FUNCTIONAL LIVER MARKERS	
Bilirubin	↑ in various liver diseases (eg, biliary obstruction, alcoholic or viral hepatitis, cirrhosis), hemolysis
Albumin	↓ in advanced liver disease (marker of liver's biosynthetic function)
Prothrombin time	↑ in advanced liver disease (↓ production of clotting factors, thereby measuring the liver's biosynthetic function)
Platelets	↓ in advanced liver disease (↓ thrombopoietin, liver sequestration) and portal hypertension (splenomegaly/splenic sequestration)

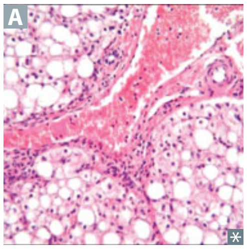
Reye syndrome	Rare, often fatal childhood hepatic encephalopathy. Findings: mitochondrial abnormalities, fatty liver (microvesicular fatty change), hypoglycemia, vomiting, hepatomegaly, coma. Associated with viral infection (especially VZV and influenza B) that has been treated with aspirin. Mechanism: aspirin metabolites ↓ β-oxidation by reversible inhibition of mitochondrial enzymes. Avoid aspirin in children, except in those with Kawasaki disease.

Alcoholic liver disease

Hepatic steatosis	Macrovesicular fatty change A that may be reversible with alcohol cessation.	
Alcoholic hepatitis	Requires sustained, long-term consumption. Swollen and necrotic hepatocytes with neutrophilic infiltration. Mallory bodies B (intracytoplasmic eosinophilic inclusions of damaged keratin filaments).	Make a to**AST** with alcohol: **AST** > ALT (ratio usually > 2:1).
Alcoholic cirrhosis	Final and usually irreversible form. Regenerative nodules surrounded by fibrous bands in response to chronic liver injury → portal hypertension and end-stage liver disease. Sclerosis around central vein (arrows in C) may be seen in early disease.	



Nonalcoholic fatty liver disease



Metabolic syndrome (insulin resistance); obesity → fatty infiltration of hepatocytes A → cellular "ballooning" and eventual necrosis. May cause cirrhosis and HCC. Independent of alcohol use.

A**L**T > AST (**L**ipids)

Hepatic encephalopathy

Cirrhosis → portosystemic shunts → ↓ NH$_3$ metabolism → neuropsychiatric dysfunction. Reversible neuropsychiatric dysfunction ranging from disorientation/asterixis (mild) to difficult arousal or coma (severe). Triggers:

- ↑ NH$_3$ production and absorption (due to dietary protein, GI bleed, constipation, infection).
- ↓ NH$_3$ removal (due to renal failure, diuretics, bypassed hepatic blood flow post-TIPS).

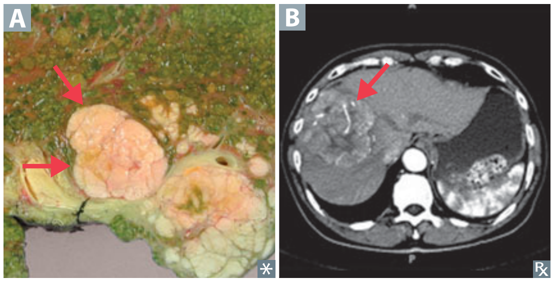
Treatment: lactulose (↑ NH$_4^+$ generation) and rifaximin or neomycin (↓ NH$_3$ producing gut bacteria).

Hepatocellular carcinoma/hepatoma

Most common 1° malignant tumor of liver in adults A. Associated with HBV (+/– cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and nonalcoholic fatty liver disease, autoimmune disease, hemochromatosis, α_1-antitrypsin deficiency) and specific carcinogens (eg, aflatoxin from *Aspergillus*). May lead to Budd-Chiari syndrome.

Findings: jaundice, tender hepatomegaly, ascites, polycythemia, anorexia. Spreads hematogenously.

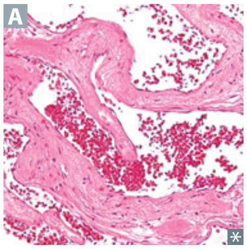
Diagnosis: ↑ α-fetoprotein; ultrasound or contrast CT/MRI B, biopsy.



Other liver tumors

Cavernous hemangioma

Common, benign liver tumor A; typically occurs at age 30–50 years. Biopsy contraindicated because of risk of hemorrhage.



Hepatic adenoma

Rare, benign liver tumor, often related to oral contraceptive or anabolic steroid use; may regress spontaneously or rupture (abdominal pain and shock).

Angiosarcoma

Malignant tumor of endothelial origin; associated with exposure to arsenic, vinyl chloride.

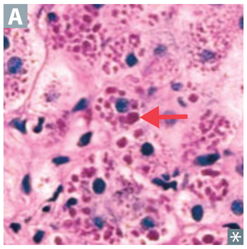
Metastases

GI malignancies, breast and lung cancer. Most common overall; metastases are rarely solitary.

Budd-Chiari syndrome

Thrombosis or compression of hepatic veins with centrilobular congestion and necrosis → congestive liver disease (hepatomegaly, ascites, varices, abdominal pain, liver failure). Absence of JVD. Associated with hypercoagulable states, polycythemia vera, postpartum state, HCC. May cause nutmeg liver (mottled appearance).

α_1-antitrypsin deficiency

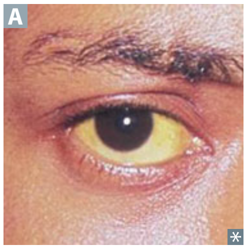


Misfolded gene product protein aggregates in hepatocellular ER → cirrhosis with PAS ⊕ globules A in liver. Codominant trait.

Often presents in young patients with liver damage and dyspnea without a history of smoking.

In lungs, ↓ α_1-antitrypsin → uninhibited elastase in alveoli → ↓ elastic tissue → panacinar emphysema.

Jaundice



Abnormal yellowing of the skin and/or sclera A due to bilirubin deposition. Hyperbilirubinemia 2° to ↑ production or ↓ disposition (impaired hepatic uptake, conjugation, excretion).

HOT Liver—common causes of increased levels of bilirubin:
Hemolysis
Obstruction
Tumor
Liver disease

Unconjugated (indirect) hyperbilirubinemia	Hemolytic, physiologic (newborns), Crigler-Najjar, Gilbert syndrome.
Conjugated (direct) hyperbilirubinemia	Biliary tract obstruction: gallstones, cholangiocarcinoma, pancreatic or liver cancer, liver fluke. Biliary tract disease: ▪ 1° sclerosing cholangitis ▪ 1° biliary cholangitis Excretion defect: Dubin-Johnson syndrome, Rotor syndrome.
Mixed (direct and indirect) hyperbilirubinemia	Hepatitis, cirrhosis.

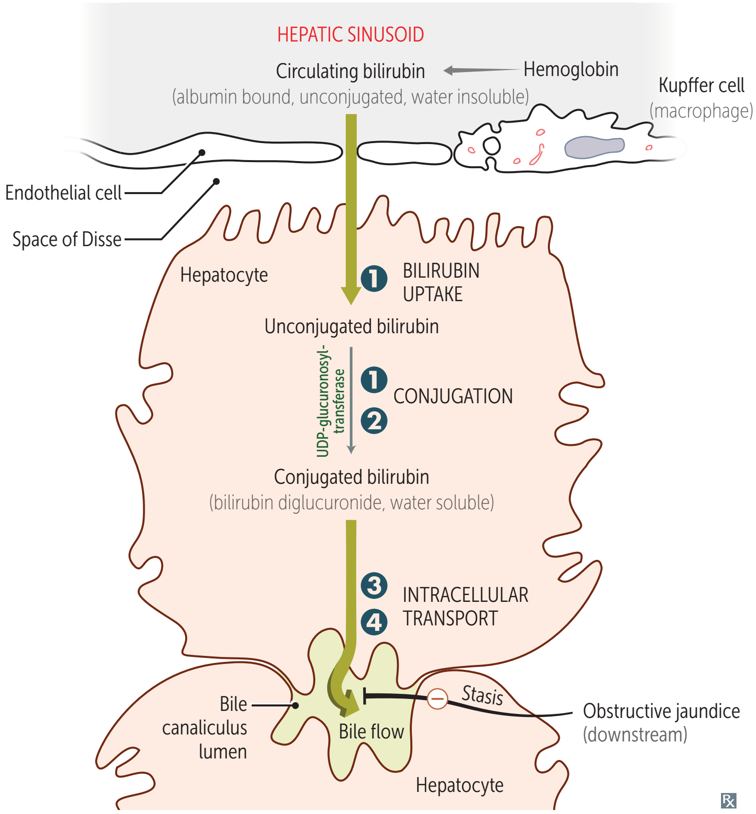
Physiologic neonatal jaundice

At birth, immature UDP-glucuronosyltransferase → unconjugated hyperbilirubinemia → jaundice/kernicterus (deposition of unconjugated, lipid-soluble bilirubin in the brain, particularly basal ganglia).

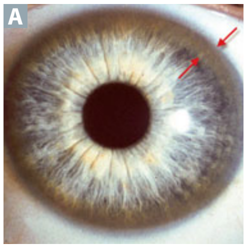
Occurs after first 24 hours of life and usually resolves without treatment in 1–2 weeks.

Treatment: phototherapy (non-UV) isomerizes unconjugated bilirubin to water-soluble form.

Hereditary hyperbilirubinemias	All autosomal recessive.	
❶ Gilbert syndrome	Mildly ↓ UDP-glucuronosyltransferase conjugation and impaired bilirubin uptake. Asymptomatic or mild jaundice usually with stress, illness, or fasting. ↑ unconjugated bilirubin without overt hemolysis. Bilirubin ↑ with fasting and stress.	Relatively common, benign condition.
❷ Crigler-Najjar syndrome, type I	Absent UDP-glucuronosyltransferase. Presents early in life; patients die within a few years. Findings: jaundice, kernicterus (bilirubin deposition in brain), ↑ unconjugated bilirubin. Treatment: plasmapheresis and phototherapy.	Type II is less severe and responds to phenobarbital, which ↑ liver enzyme synthesis.
❸ Dubin-Johnson syndrome	Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black liver. Benign.	❹ **Rotor syndrome** is similar, but milder in presentation without black liver. Due to impaired hepatic uptake and excretion.


HEPATIC SINUSOID
Circulating bilirubin
(albumin bound, unconjugated, water insoluble)
Hemoglobin
Kupffer cell
(macrophage)
Endothelial cell
Space of Disse
Hepatocyte
❶ BILIRUBIN UPTAKE
Unconjugated bilirubin
UDP-glucuronosyl-transferase
❶ ❷ CONJUGATION
Conjugated bilirubin
(bilirubin diglucuronide, water soluble)
❸ ❹ INTRACELLULAR TRANSPORT
Bile canaliculus lumen
Bile flow
Stasis
Obstructive jaundice
(downstream)
Hepatocyte

Wilson disease (hepatolenticular degeneration)

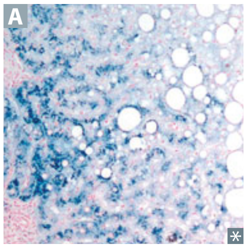


Autosomal recessive mutations in hepatocyte copper-transporting ATPase (*ATP7B* gene; chromosome 13) → ↓ copper excretion into bile and incorporation into apoceruloplasmin → ↓ serum ceruloplasmin. Copper accumulates, especially in liver, brain, cornea, kidneys; ↑ urine copper.

Presents before age 40 with liver disease (eg, hepatitis, acute liver failure, cirrhosis), neurologic disease (eg, dysarthria, dystonia, tremor, parkinsonism), psychiatric disease, Kayser-Fleischer rings (deposits in Descemet membrane of cornea) A, hemolytic anemia, renal disease (eg, Fanconi syndrome).

Treatment: chelation with penicillamine or trientine, oral zinc.

Hemochromatosis



Recessive mutations in *HFE* gene (C282Y > H63D, chromosome 6, associated with HLA-A3) → abnormal iron sensing and ↑ intestinal absorption (↑ ferritin, ↑ iron, ↓ TIBC → ↑ transferrin saturation). Iron overload can also be 2° to chronic transfusion therapy (eg, β-thalassemia major). Iron accumulates, especially in liver, pancreas, skin, heart, pituitary, joints. Hemosiderin (iron) can be identified on liver MRI or biopsy with Prussian blue stain A.

Presents after age 40 when total body iron > 20 g; iron loss through menstruation slows progression in women. Classic triad of cirrhosis, diabetes mellitus, skin pigmentation ("bronze diabetes"). Also causes restrictive cardiomyopathy (classic) or dilated cardiomyopathy (reversible), hypogonadism, arthropathy (calcium pyrophosphate deposition; especially metacarpophalangeal joints). HCC is common cause of death.

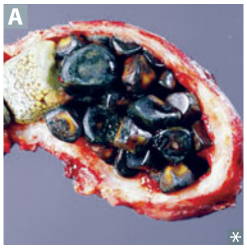
Treatment: repeated phlebotomy, chelation with deferasirox, deferoxamine, oral deferiprone.

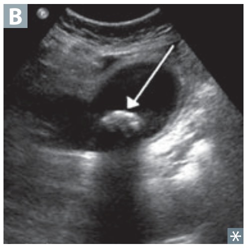
Biliary tract disease

May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly. Typically with cholestatic pattern of LFTs (↑ conjugated bilirubin, ↑ cholesterol, ↑ ALP).

	PATHOLOGY	EPIDEMIOLOGY	ADDITIONAL FEATURES
Primary sclerosing cholangitis	Unknown cause of concentric "onion skin" bile duct fibrosis → alternating strictures and dilation with "beading" of intra- and extrahepatic bile ducts on ERCP, magnetic resonance cholangiopancreatography (MRCP).	Classically in middle-aged men with IBD.	Associated with ulcerative colitis. p-ANCA ⊕. ↑ IgM. Can lead to 2° biliary cholangitis. ↑ risk of cholangiocarcinoma and gallbladder cancer.
Primary biliary cholangitis	Autoimmune reaction → lymphocytic infiltrate + granulomas → destruction of intralobular bile ducts.	Classically in middle-aged women.	Anti-mitochondrial antibody ⊕, ↑ IgM. Associated with other autoimmune conditions (eg, Sjögren syndrome, Hashimoto thyroiditis, CREST, rheumatoid arthritis, celiac disease).
Secondary biliary cholangitis	Extrahepatic biliary obstruction → ↑ pressure in intrahepatic ducts → injury/ fibrosis and bile stasis.	Patients with known obstructive lesions (gallstones, biliary strictures, pancreatic carcinoma).	May be complicated by ascending cholangitis.

Gallstones (cholelithiasis)





↑ cholesterol and/or bilirubin, ↓ bile salts, and gallbladder stasis all cause stones.

2 types of stones:

- Cholesterol stones (radiolucent with 10–20% opaque due to calcifications)—80% of stones. Associated with obesity, Crohn disease, advanced age, estrogen therapy, multiparity, rapid weight loss, Native American origin.
- Pigment stones A (black = radiopaque, Ca^{2+} bilirubinate, hemolysis; brown = radiolucent, infection). Associated with Crohn disease, chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN).

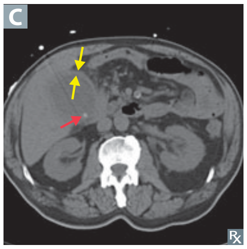
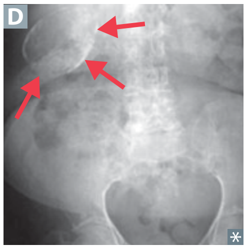
Most common complication is cholecystitis; can also cause acute pancreatitis, ascending cholangitis.

Risk factors (4 F's):

1. Female
2. Fat
3. Fertile (pregnant)
4. Forty

Diagnose with ultrasound B. Treat with elective cholecystectomy if symptomatic.

Can cause fistula between gallbladder and GI tract → air in biliary tree (pneumobilia) → passage of gallstones into intestinal tract → obstruction of ileocecal valve (gallstone ileus).

RELATED PATHOLOGIES	CHARACTERISTICS
Biliary colic	Associated with nausea/vomiting and dull RUQ pain. Neurohormonal activation (eg, by CCK after a fatty meal) triggers contraction of gallbladder, forcing stone into cystic duct. Labs are normal, ultrasound shows cholelithiasis.
Choledocholithiasis	Presence of gallstone(s) in common bile duct, often leading to elevated ALP, GGT, direct bilirubin, and/or AST/ALT.
Cholecystitis 	Acute or chronic inflammation of gallbladder usually from cholelithiasis (stone at neck of gallbladder [red arrow in C] with gallbladder wall thickening [yellow arrows]). Calculous cholecystitis: most common type; due to gallstone impaction in the cystic duct resulting in inflammation; can produce 2° infection. Acalculous cholecystitis: due to gallbladder stasis, hypoperfusion, or infection (CMV); seen in critically ill patients. Murphy sign: inspiratory arrest on RUQ palpation due to pain. ↑ ALP if bile duct becomes involved (eg, ascending cholangitis). Diagnose with ultrasound or cholescintigraphy (HIDA scan). Failure to visualize gallbladder on HIDA scan suggests obstruction.
Porcelain gallbladder 	Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging D. Treatment: prophylactic cholecystectomy due to high rates of gallbladder cancer (mostly adenocarcinoma).
Ascending cholangitis	Infection of biliary tree usually due to obstruction that leads to stasis/bacterial overgrowth. Charcot triad of cholangitis: ▪ Jaundice ▪ Fever ▪ RUQ pain Reynolds pentad adds: ▪ Altered mental status ▪ Shock (hypotension)

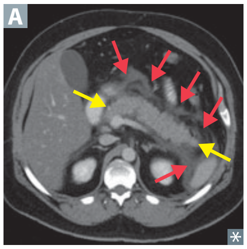
Acute pancreatitis

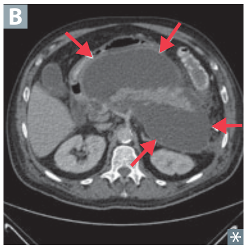
Autodigestion of pancreas by pancreatic enzymes (A shows pancreas [yellow arrows] surrounded by edema [red arrows]).

Causes: Idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune disease, Scorpion sting, Hypercalcemia/Hypertriglyceridemia (> 1000 mg/dL), ERCP, Drugs (eg, sulfa drugs, NRTIs, protease inhibitors). **I GET SMASHED**.

Diagnosis by 2 of 3 criteria: acute epigastric pain often radiating to the back, ↑ serum amylase or lipase (more specific) to 3× upper limit of normal, or characteristic imaging findings.

Complications: pseudocyst B (lined by granulation tissue, not epithelium), necrosis, hemorrhage, infection, organ failure (ARDS, shock, renal failure), hypocalcemia (precipitation of Ca^{2+} soaps).



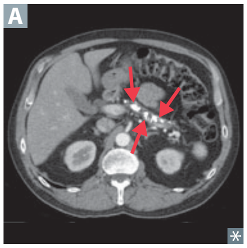


Chronic pancreatitis

Chronic inflammation, atrophy, calcification of the pancreas A. Major causes are alcohol abuse and idiopathic. Complications include pancreatic insufficiency and pseudocysts.

Pancreatic insufficiency may manifest with steatorrhea, fat-soluble vitamin deficiency, diabetes mellitus.

Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).



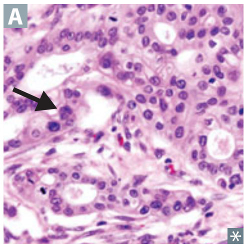
Pancreatic adenocarcinoma

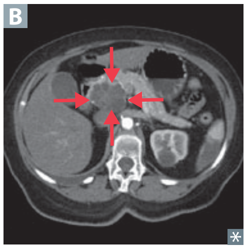
Very aggressive tumor arising from pancreatic ducts (disorganized glandular structure with cellular infiltration A); often metastatic at presentation, with average survival ~ 1 year after diagnosis. Tumors more common in pancreatic head B (→ obstructive jaundice). Associated with CA 19-9 tumor marker (also CEA, less specific).

Risk factors:
- Tobacco use
- Chronic pancreatitis (especially > 20 years)
- Diabetes
- Age > 50 years
- Jewish and African-American males

Often presents with:
- Abdominal pain radiating to back
- Weight loss (due to malabsorption and anorexia)
- Migratory thrombophlebitis—redness and tenderness on palpation of extremities (Trousseau syndrome)
- Obstructive jaundice with palpable, nontender gallbladder (Courvoisier sign)

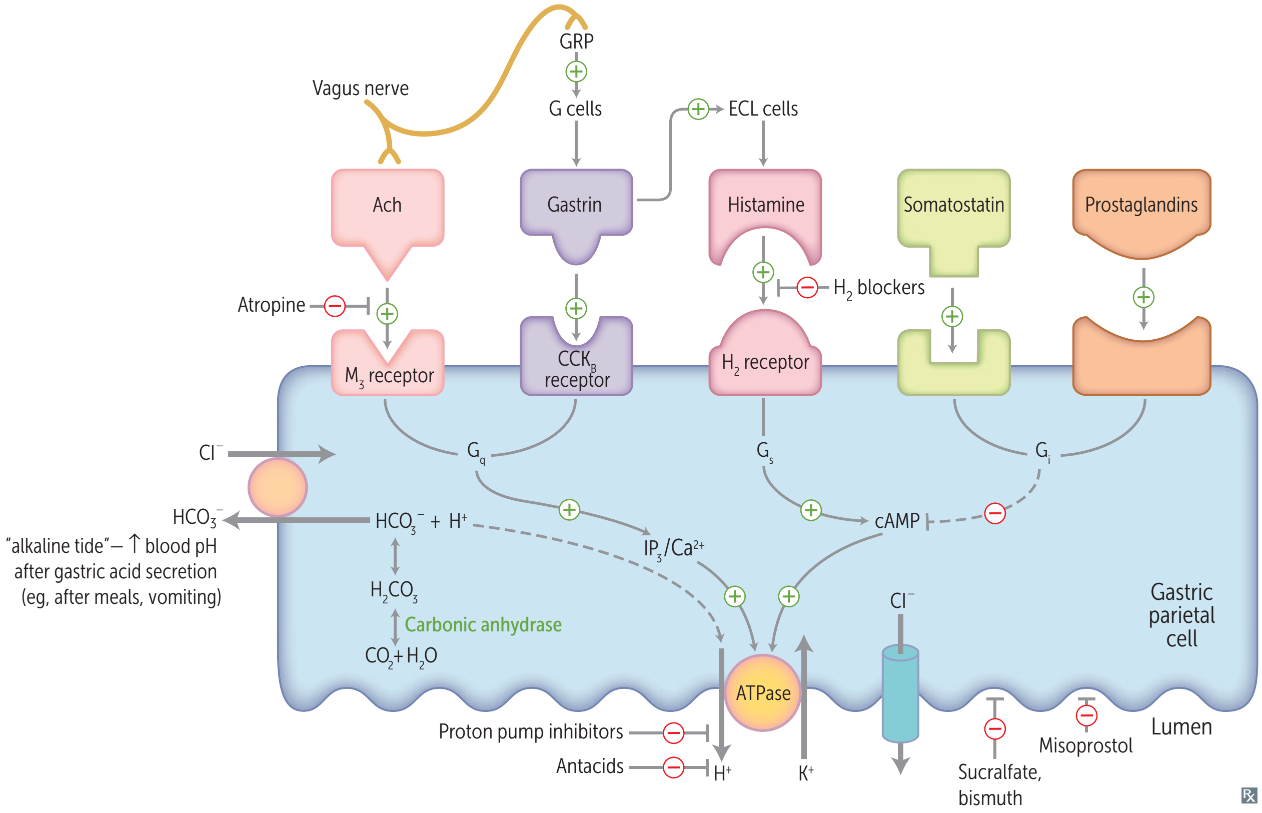
Treatment: Whipple procedure, chemotherapy, radiation therapy.





▶ GASTROINTESTINAL—PHARMACOLOGY

Acid suppression therapy


GRP
Vagus nerve
G cells
ECL cells
Ach
Gastrin
Histamine
Somatostatin
Prostaglandins
Atropine
H2 blockers
M3 receptor
CCKB receptor
H2 receptor
Cl⁻
Gq
Gs
Gi
HCO3⁻
"alkaline tide"—↑ blood pH after gastric acid secretion (eg, after meals, vomiting)
HCO3⁻ + H⁺
IP3/Ca2+
cAMP
H2CO3
Carbonic anhydrase
CO2+H2O
Cl⁻
Gastric parietal cell
ATPase
Proton pump inhibitors
Antacids
H⁺
K⁺
Sucralfate, bismuth
Misoprostol
Lumen

H_2 blockers	Cimeti**dine**, raniti**dine**, famoti**dine**, nizati**dine**.	Take H_2 blockers before you **dine**. Think "**table for 2**" to remember **H_2**.
MECHANISM	Reversible block of histamine H_2-receptors → ↓ H^+ secretion by parietal cells.	
CLINICAL USE	Peptic ulcer, gastritis, mild esophageal reflux.	
ADVERSE EFFECTS	Cimetidine is a potent inhibitor of cytochrome P-450 (multiple drug interactions); it also has antiandrogenic effects (prolactin release, gynecomastia, impotence, ↓ libido in males); can cross blood-brain barrier (confusion, dizziness, headaches) and placenta. Both cimetidine and ranitidine ↓ renal excretion of creatinine. Other H_2 blockers are relatively free of these effects.	

Proton pump inhibitors	Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole.
MECHANISM	Irreversibly inhibit H^+/K^+ ATPase in stomach parietal cells.
CLINICAL USE	Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome, component of therapy for *H pylori*, stress ulcer prophylaxis.
ADVERSE EFFECTS	↑ risk of *C difficile* infection, pneumonia. ↓ serum Mg^{2+} with long-term use.

Antacid use	Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying. All can cause hypokalemia. Overuse can also cause the following problems.	
Aluminum hydroxide	Constipation and hypophosphatemia; proximal muscle weakness, osteodystrophy, seizures	Aluminimum amount of feces.
Calcium carbonate	Hypercalcemia (milk-alkali syndrome), rebound acid ↑	Can chelate and ↓ effectiveness of other drugs (eg, tetracycline).
Magnesium hydroxide	Diarrhea, hyporeflexia, hypotension, cardiac arrest	Mg^{2+} = Must go to the bathroom.

Bismuth, sucralfate

MECHANISM	Bind to ulcer base, providing physical protection and allowing HCO_3^- secretion to reestablish pH gradient in the mucous layer. Require acidic environment; usually not given with PPIs/H_2 blockers.
CLINICAL USE	↑ ulcer healing, travelers' diarrhea.

Misoprostol

MECHANISM	A PGE_1 analog. ↑ production and secretion of gastric mucous barrier, ↓ acid production.
CLINICAL USE	Prevention of NSAID-induced peptic ulcers (NSAIDs block PGE_1 production). Also used off-label for induction of labor (ripens cervix).
ADVERSE EFFECTS	Diarrhea. Contraindicated in women of childbearing potential (abortifacient).

Octreotide

MECHANISM	Long-acting somatostatin analog; inhibits secretion of various splanchnic vasodilatory hormones.
CLINICAL USE	Acute variceal bleeds, acromegaly, VIPoma, carcinoid tumors.
ADVERSE EFFECTS	Nausea, cramps, steatorrhea. ↑ risk of cholelithiasis due to CCK inhibition.

Sulfasalazine

MECHANISM	A combination of sulfapyridine (antibacterial) and 5-aminosalicylic acid (anti-inflammatory). Activated by colonic bacteria.
CLINICAL USE	Ulcerative colitis, Crohn disease (colitis component).
ADVERSE EFFECTS	Malaise, nausea, sulfonamide toxicity, reversible oligospermia.

Loperamide

MECHANISM	Agonist at μ-opioid receptors; slows gut motility. Poor CNS penetration (low addictive potential).
CLINICAL USE	Diarrhea.
ADVERSE EFFECTS	Constipation, nausea.

Ondansetron

MECHANISM	5-HT$_3$ antagonist; ↓ vagal stimulation. Powerful central-acting antiemetic.
CLINICAL USE	Control vomiting postoperatively and in patients undergoing cancer chemotherapy.
ADVERSE EFFECTS	Headache, constipation, QT interval prolongation, serotonin syndrome.

Metoclopramide

MECHANISM	D$_2$ receptor antagonist. ↑ resting tone, contractility, LES tone, motility, promotes gastric emptying. Does not influence colon transport time.
CLINICAL USE	Diabetic and postsurgery gastroparesis, antiemetic, persistent GERD..
ADVERSE EFFECTS	↑ parkinsonian effects, tardive dyskinesia. Restlessness, drowsiness, fatigue, depression, diarrhea. Drug interaction with digoxin and diabetic agents. Contraindicated in patients with small bowel obstruction or Parkinson disease (due to D$_2$-receptor blockade).

Orlistat

MECHANISM	Inhibits gastric and pancreatic lipase → ↓ breakdown and absorption of dietary fats.
CLINICAL USE	Weight loss.
ADVERSE EFFECTS	Steatorrhea, ↓ absorption of fat-soluble vitamins.

Laxatives	Indicated for constipation or patients on opiates requiring a bowel regimen
Bulk-forming laxatives	Psyllium, methylcellulose
MECHANISM	Soluble fibers; draw water into gut lumen, forming a viscous liquid that promotes peristalsis
ADVERSE EFFECTS	Bloating
Osmotic laxatives	Magnesium hydroxide, magnesium citrate, polyethylene glycol, lactulose
MECHANISM	Provide osmotic load to draw water into GI lumen Lactulose also treats hepatic encephalopathy because gut flora degrade it into metabolites (lactic acid, acetic acid) that promote nitrogen excretion as NH$_4^+$
ADVERSE EFFECTS	Diarrhea, dehydration; may be abused by bulimics
Stimulants	Senna
MECHANISM	Enteric nerve stimulation → colonic contraction
ADVERSE EFFECTS	Diarrhea, melanosis coli
Emollients	Docusate
MECHANISM	Osmotic draw into lumen → ↑ water absorption by stool
ADVERSE EFFECTS	Diarrhea

Aprepitant

MECHANISM	Substance P antagonist. Blocks NK$_1$ receptors in brain.
CLINICAL USE	Antiemetic for chemotherapy-induced nausea and vomiting.

NOTES

HIGH-YIELD SYSTEMS

Hematology and Oncology

"Of all that is written, I love only what a person has written with his own blood."

—Friedrich Nietzsche

"I used to get stressed out, but my cancer has put everything into perspective."

—Delta Goodrem

"The best blood will at some time get into a fool or a mosquito."

—Austin O'Malley

"Carcinoma works cunningly from the inside out. Detection and treatment often work more slowly and gropingly, from the outside in."

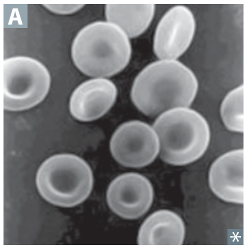
—Christopher Hitchens

Study tip: When reviewing oncologic drugs, focus on mechanisms and side effects rather than details of clinical uses, which may be lower yield.

- ▸ Anatomy 386
- ▸ Physiology 389
- ▸ Pathology 394
- ▸ Pharmacology 413

▶ HEMATOLOGY AND ONCOLOGY—ANATOMY

Erythrocyte



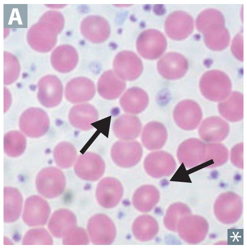
Carries O_2 to tissues and CO_2 to lungs. Anucleate and lacks organelles; biconcave A, with large surface area-to-volume ratio for rapid gas exchange. Life span of 120 days. Source of energy is glucose (90% used in glycolysis, 10% used in HMP shunt). Membrane contains Cl^-/HCO_3^- antiporter, which allows RBCs to export HCO_3^- and transport CO_2 from the periphery to the lungs for elimination.

Eryth = red; *cyte* = cell.

Erythrocytosis = polycythemia = ↑ hematocrit.
Anisocytosis = varying sizes.
Poikilocytosis = varying shapes.

Reticulocyte = immature RBC; reflects erythroid proliferation.
Bluish color on Wright-Giemsa stain of reticulocytes represents residual ribosomal RNA.

Thrombocyte (platelet)



Involved in 1° hemostasis. Small cytoplasmic fragment A derived from megakaryocytes. Life span of 8–10 days. When activated by endothelial injury, aggregates with other platelets and interacts with fibrinogen to form platelet plug. Contains dense granules (ADP, Ca^{2+}) and α granules (vWF, fibrinogen, fibronectin). Approximately ⅓ of platelet pool is stored in the spleen.

Thrombocytopenia or ↓ platelet function results in petechiae.
vWF receptor: GpIb.
Fibrinogen receptor: GpIIb/IIIa.

Leukocyte

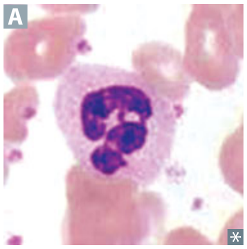
Divided into granulocytes (neutrophil, eosinophil, basophil, mast cell) and mononuclear cells (monocytes, lymphocytes).

WBC differential count from highest to lowest (normal ranges per USMLE):
- **N**eutrophils (~ 60%)
- **L**ymphocytes (~ 30%)
- **M**onocytes (~ 6%)
- **E**osinophils (~ 3%)
- **B**asophils (~ 1%)

Leuk = white; *cyte* = cell.

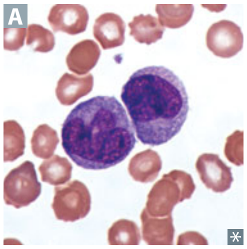
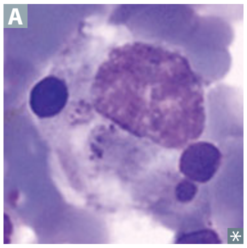
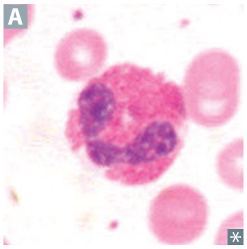
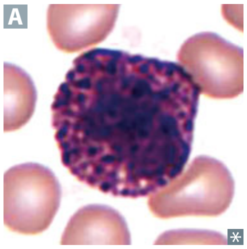
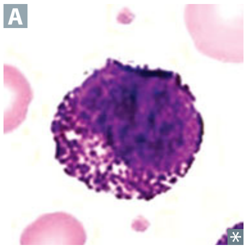
Neutrophils **L**ike **M**aking **E**verything **B**etter.

Neutrophil

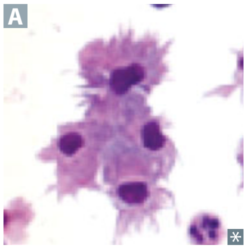


Acute inflammatory response cell. Increased in bacterial infections. Phagocytic. Multilobed nucleus A. Specific granules contain leukocyte alkaline phosphatase (LAP), collagenase, lysozyme, and lactoferrin. Azurophilic granules (lysosomes) contain proteinases, acid phosphatase, myeloperoxidase, and β-glucuronidase.

Hypersegmented neutrophils (nucleus has 6+ lobes) are seen in vitamin B_{12}/ folate deficiency.
↑ band cells (immature neutrophils) reflect states of ↑ myeloid proliferation (bacterial infections, CML).
Important neutrophil chemotactic agents: C5a, IL-8, LTB_4, kallikrein, platelet-activating factor.

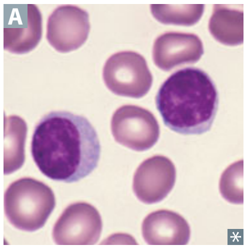
Monocyte 	Differentiates into macrophage in tissues. Large, kidney-shaped nucleus A. Extensive "frosted glass" cytoplasm.	*Mono* = one (nucleus); *cyte* = cell. Found in blood.
Macrophage 	Phagocytoses bacteria, cellular debris, and senescent RBCs. Long life in tissues. Macrophages differentiate from circulating blood monocytes A. Activated by γ-interferon. Can function as antigen-presenting cell via MHC II.	*Macro* = large; *phage* = eater. Found in tissue. Name differs in each tissue type (eg, Kupffer cells in the liver, histiocytes in connective tissue). Important component of granuloma formation (eg, TB, sarcoidosis). Lipid A from bacterial LPS binds CD14 on macrophages to initiate septic shock.
Eosinophil 	Defends against helminthic infections (major basic protein). Bilobate nucleus. Packed with large eosinophilic granules of uniform size A. Highly phagocytic for antigen-antibody complexes. Produces histaminase, major basic protein (MBP, a helminthotoxin), eosinophil peroxidase, eosinophil cationic protein, and eosinophil-derived neurotoxin.	*Eosin* = pink dye; *philic* = loving. Causes of eosinophilia = **NAACP**: **N**eoplasia **A**sthma **A**llergic processes **C**hronic adrenal insufficiency **P**arasites (invasive)
Basophil 	Mediates allergic reaction. Densely basophilic granules A contain heparin (anticoagulant) and histamine (vasodilator). Leukotrienes synthesized and released on demand.	**Baso**philic—staining readily with **basic** stains. Basophilia is uncommon, but can be a sign of myeloproliferative disease, particularly CML.
Mast cell 	Mediates allergic reaction in local tissues. Mast cells contain basophilic granules A and originate from the same precursor as basophils but are not the same cell type. Can bind the Fc portion of IgE to membrane. IgE cross-links upon antigen binding → degranulation → release of histamine, heparin, tryptase, and eosinophil chemotactic factors.	Involved in type I hypersensitivity reactions. Cromolyn sodium prevents mast cell degranulation (used for asthma prophylaxis).

Dendritic cell



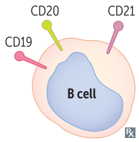
Highly phagocytic antigen-presenting cell (APC) A. Functions as link between innate and adaptive immune systems. Expresses MHC class II and Fc receptors on surface. Called Langerhans cell in the skin.

Lymphocyte



Refers to B cells, T cells, and NK cells. B cells and T cells mediate adaptive immunity. NK cells are part of the innate immune response. Round, densely staining nucleus with small amount of pale cytoplasm A.

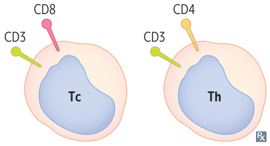
B cell



Part of humoral immune response. Originates from stem cells in bone marrow and matures in marrow. Migrates to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells (which produce antibodies) and memory cells. Can function as an APC via MHC II.

B = Bone marrow.

T cell



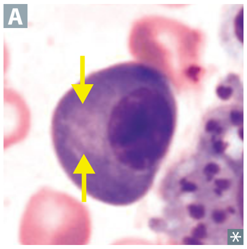
Mediates cellular immune response. Originates from stem cells in the bone marrow, but matures in the thymus. T cells differentiate into cytotoxic T cells (express CD8, recognize MHC I), helper T cells (express CD4, recognize MHC II), and regulatory T cells. CD28 (costimulatory signal) necessary for T-cell activation. The majority of circulating lymphocytes are T cells (80%).

T is for Thymus.

CD4+ helper T cells are the primary target of HIV.

Rule of 8: MHC II × CD4 = 8;
MHC I × CD8 = 8.

Plasma cell



Produces large amounts of antibody specific to a particular antigen. "Clock-face" chromatin distribution and eccentric nucleus, abundant RER, and well-developed Golgi apparatus (arrows in A). Found in bone marrow and normally do not circulate in peripheral blood.

Multiple myeloma is a plasma cell cancer.

▶ HEMATOLOGY AND ONCOLOGY—PHYSIOLOGY

Fetal erythropoiesis

Fetal erythropoiesis occurs in:

- **Y**olk sac (3–8 weeks)
- **L**iver (6 weeks–birth)
- **S**pleen (10–28 weeks)
- **B**one marrow (18 weeks to adult)

Young **L**iver **S**ynthesizes **B**lood.

Hemoglobin development

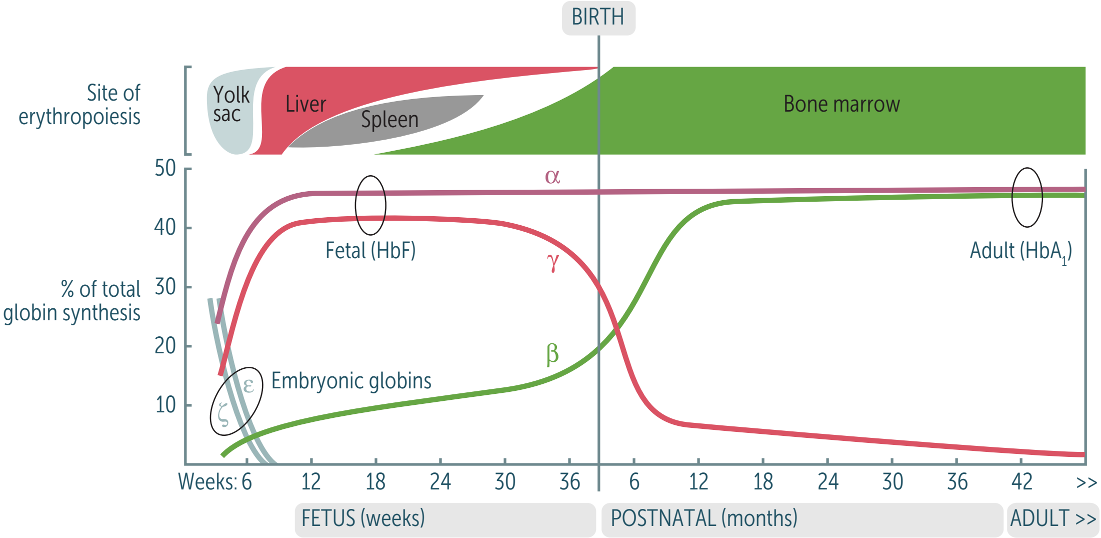
Embryonic globins: ζ and ε.

Fetal hemoglobin (HbF) = $\alpha_2\gamma_2$.

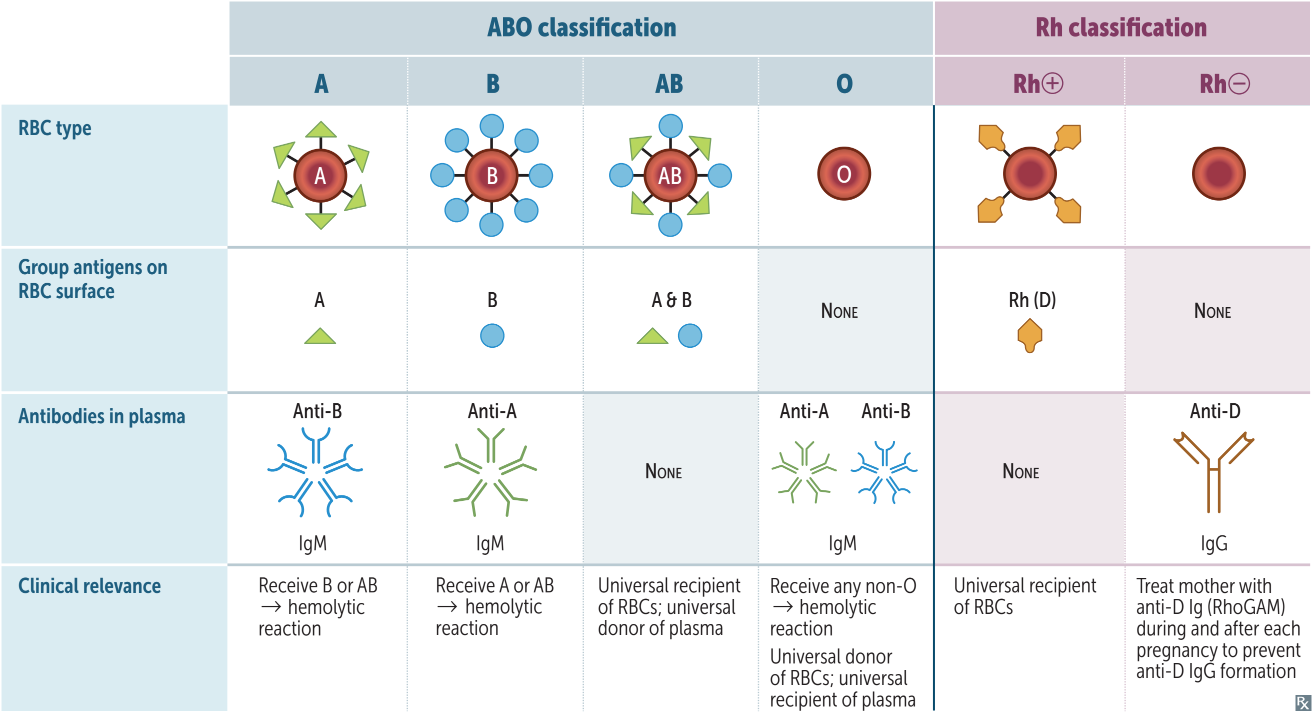
Adult hemoglobin (HbA_1) = $\alpha_2\beta_2$.

HbF has higher affinity for O_2 due to less avid binding of 2,3-BPG, allowing HbF to extract O_2 from maternal hemoglobin (HbA_1 and HbA_2) across the placenta. HbA_2 ($\alpha_2\delta_2$) is a form of adult hemoglobin present in small amounts.

From fetal to adult hemoglobin:
Alpha **A**lways; **G**amma **G**oes, **B**ecomes **B**eta.



Blood groups



	ABO classification				Rh classification	
	A	**B**	**AB**	**O**	**Rh⊕**	**Rh⊖**
RBC type	A	B	AB	O		
Group antigens on RBC surface	A ▲	B ●	A & B ▲ ●	NONE	Rh (D)	NONE
Antibodies in plasma	Anti-B IgM	Anti-A IgM	NONE	Anti-A Anti-B IgM	NONE	Anti-D IgG
Clinical relevance	Receive B or AB → hemolytic reaction	Receive A or AB → hemolytic reaction	Universal recipient of RBCs; universal donor of plasma	Receive any non-O → hemolytic reaction Universal donor of RBCs; universal recipient of plasma	Universal recipient of RBCs	Treat mother with anti-D Ig (RhoGAM) during and after each pregnancy to prevent anti-D IgG formation

---

Rh hemolytic disease of the newborn

IgM does not cross placenta; IgG does cross placenta.

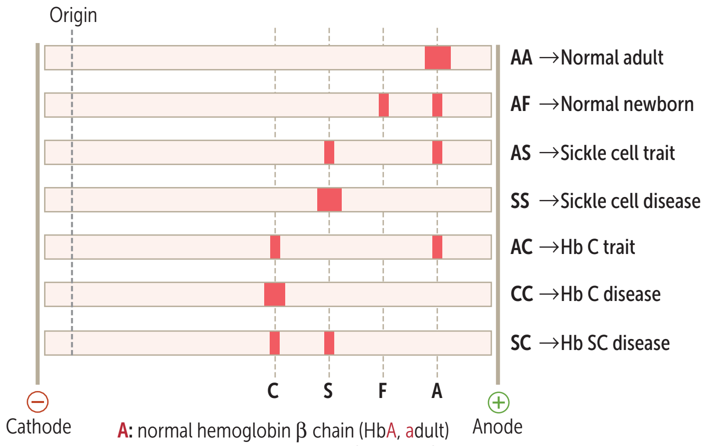
Rh⊖ mothers exposed to fetal Rh⊕ blood (often during delivery) may make anti-D IgG. In subsequent pregnancies, anti-D IgG crosses the placenta → hemolytic disease of the newborn (erythroblastosis fetalis) in the next fetus that is Rh⊕. Administration of anti-D IgG (RhoGAM) to Rh⊖ pregnant women during third trimester and early postpartum period prevents maternal anti-D IgG production.

Rh⊖ mothers have anti-D IgG only if previously exposed to Rh⊕ blood.

ABO hemolytic disease of the newborn

Usually occurs in a type O mother with a type A or B fetus. Can occur in a first pregnancy as maternal anti-A and/or anti-B IgG antibodies may be formed prior to pregnancy. Does not worsen with future pregnancies. Presents as mild jaundice in the neonate within 24 hours of birth; treatment is phototherapy or exchange transfusion.

Hemoglobin electrophoresis

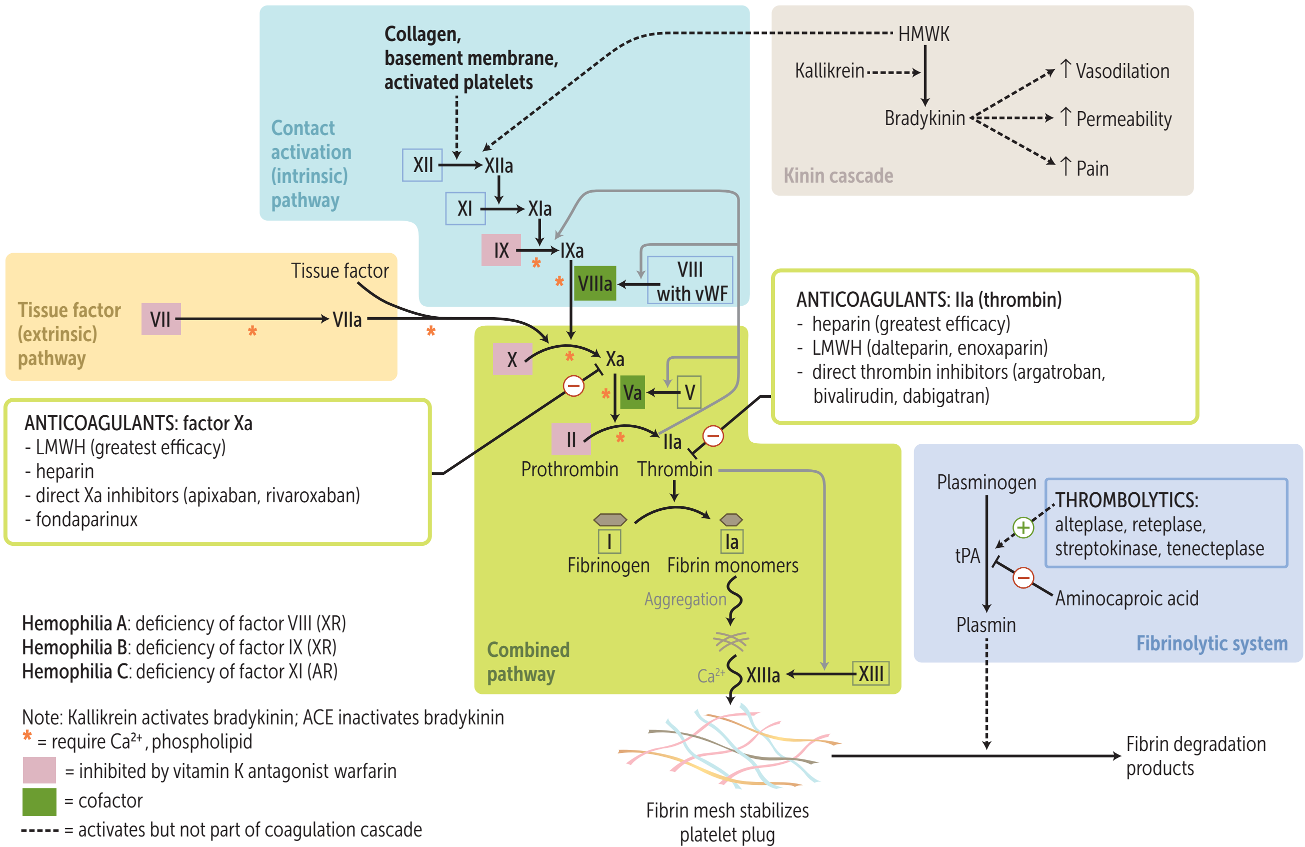

Origin
AA →Normal adult
AF →Normal newborn
AS →Sickle cell trait
SS →Sickle cell disease
AC →Hb C trait
CC →Hb C disease
SC →Hb SC disease
⊖
Cathode
C
S
F
A
⊕
Anode

A: normal hemoglobin β chain (HbA, adult)
F: normal hemoglobin γ chain (HbF, fetal)
S: sickle cell hemoglobin β chain (HbS)
C: hemoglobin C β chain (HbC)

On a gel, hemoglobin migrates from the negatively charged cathode to the positively charged anode. HbA migrates the farthest, followed by HbF, HbS, and HbC. This is because the missense mutations in HbS and HbC replace glutamic acid ⊖ with valine (neutral) and lysine ⊕, respectively, impacting the net protein charge.

A Fat Santa Claus

Coagulation and kinin pathways


Collagen, basement membrane, activated platelets
Contact activation (intrinsic) pathway
XII
XIIa
XI
XIa
IX
IXa
*
*
VIIIa
VIII with vWF
HMWK
Kallikrein
Bradykinin
↑ Vasodilation
↑ Permeability
↑ Pain
Kinin cascade
Tissue factor (extrinsic) pathway
Tissue factor
VII
VIIa
*
*
X
*
Xa
*
Va
V
II
*
IIa
Prothrombin
Thrombin
I
Ia
Fibrinogen
Fibrin monomers
Aggregation
Ca2+
XIIIa
XIII
Combined pathway
Plasminogen
tPA
Plasmin
⊕
⊖
Aminocaproic acid
Fibrinolytic system
Fibrin degradation products
Fibrin mesh stabilizes platelet plug

ANTICOAGULANTS: IIa (thrombin)
- heparin (greatest efficacy)
- LMWH (dalteparin, enoxaparin)
- direct thrombin inhibitors (argatroban, bivalirudin, dabigatran)

ANTICOAGULANTS: factor Xa
- LMWH (greatest efficacy)
- heparin
- direct Xa inhibitors (apixaban, rivaroxaban)
- fondaparinux

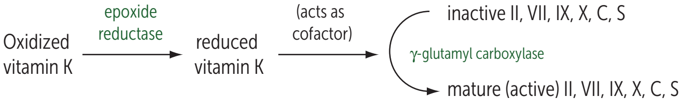
THROMBOLYTICS: alteplase, reteplase, streptokinase, tenecteplase

Hemophilia A: deficiency of factor VIII (XR)
Hemophilia B: deficiency of factor IX (XR)
Hemophilia C: deficiency of factor XI (AR)

Note: Kallikrein activates bradykinin; ACE inactivates bradykinin
* = require Ca^{2+}, phospholipid
🟪 = inhibited by vitamin K antagonist warfarin
🟩 = cofactor
----- = activates but not part of coagulation cascade
LMWH, low-molecular-weight heparin

Coagulation cascade components

Procoagulation


Oxidized vitamin K
epoxide reductase
reduced vitamin K
(acts as cofactor)
γ-glutamyl carboxylase
inactive II, VII, IX, X, C, S
mature (active) II, VII, IX, X, C, S

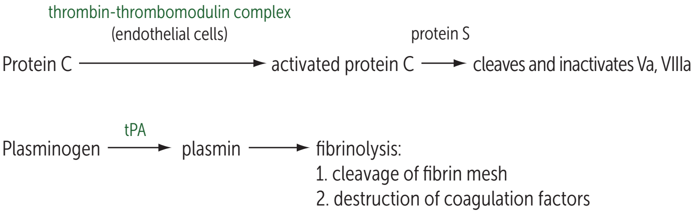
Warfarin inhibits the enzyme vitamin K epoxide reductase.

Neonates lack enteric bacteria, which produce vitamin K.

Vitamin K deficiency: ↓ synthesis of factors II, VII, IX, X, protein C, protein S.

vWF carries/protects **VIII** (**v**olks**W**agen **F**actories make gr**8** (great) cars.

Anticoagulation


thrombin-thrombomodulin complex
(endothelial cells)
Protein C
activated protein C
protein S
cleaves and inactivates Va, VIIIa
tPA
Plasminogen
plasmin
fibrinolysis:
1. cleavage of fibrin mesh
2. destruction of coagulation factors

Antithrombin inhibits activated forms of factors II, VII, IX, X, XI, XII.

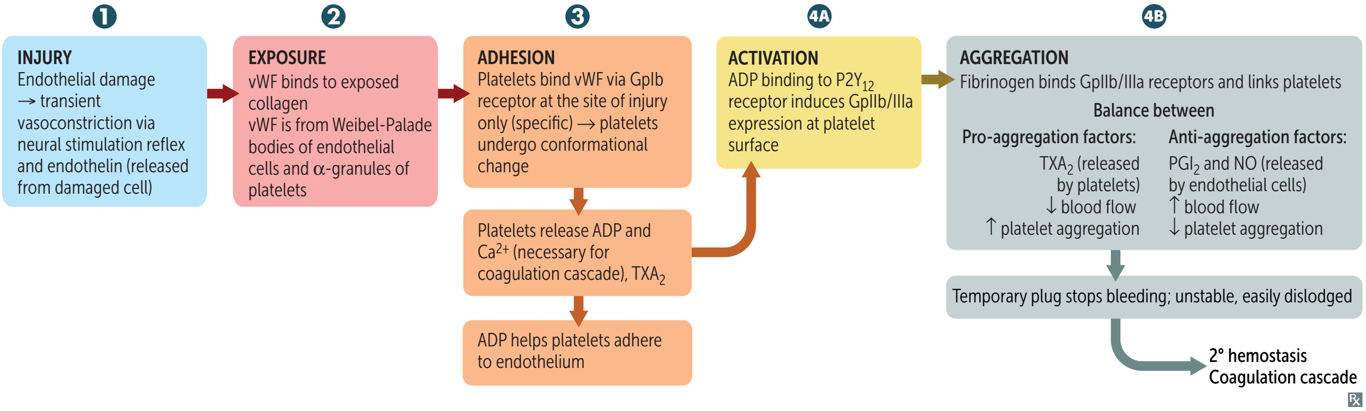
Heparin enhances the activity of antithrombin.

Principal targets of antithrombin: thrombin and factor Xa.

Factor V Leiden mutation produces a factor V resistant to inhibition by activated protein C.

tPA is used clinically as a thrombolytic.

Platelet plug formation (primary hemostasis)


❶
INJURY
Endothelial damage → transient vasoconstriction via neural stimulation reflex and endothelin (released from damaged cell)
❷
EXPOSURE
vWF binds to exposed collagen
vWF is from Weibel-Palade bodies of endothelial cells and α-granules of platelets
❸
ADHESION
Platelets bind vWF via GpIb receptor at the site of injury only (specific) → platelets undergo conformational change
Platelets release ADP and Ca^{2+} (necessary for coagulation cascade), TXA_2
ADP helps platelets adhere to endothelium
4A
ACTIVATION
ADP binding to $P2Y_{12}$ receptor induces GpIIb/IIIa expression at platelet surface
4B
AGGREGATION
Fibrinogen binds GpIIb/IIIa receptors and links platelets
Balance between
Pro-aggregation factors:
TXA_2 (released by platelets)
↓ blood flow
↑ platelet aggregation
Anti-aggregation factors:
PGI_2 and NO (released by endothelial cells)
↑ blood flow
↓ platelet aggregation
Temporary plug stops bleeding; unstable, easily dislodged
2° hemostasis
Coagulation cascade

Thrombogenesis

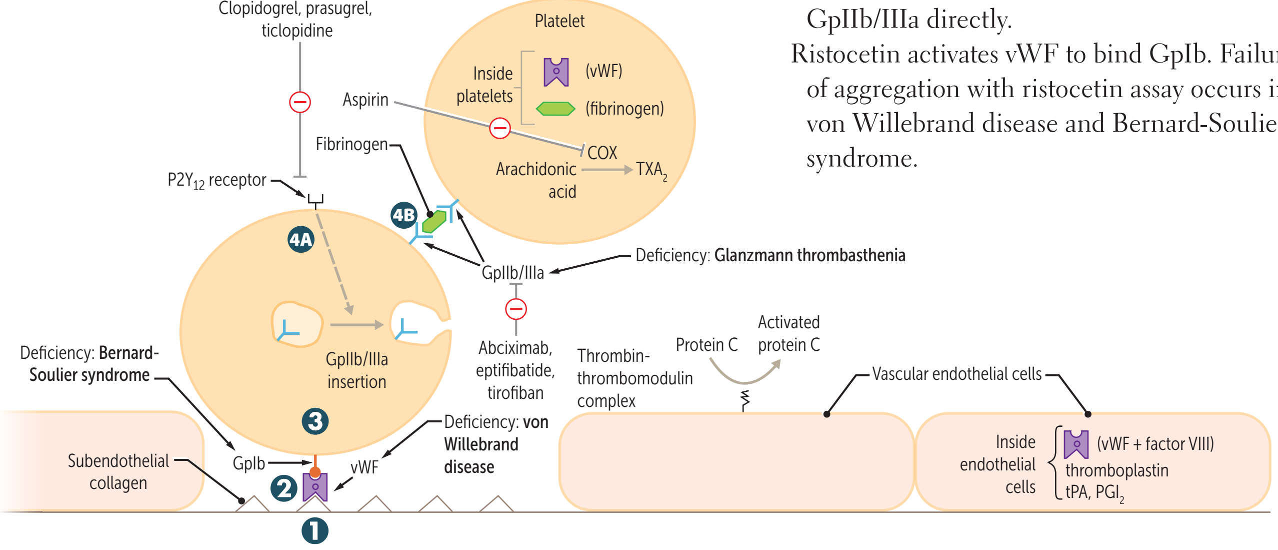
Formation of insoluble fibrin mesh.

Aspirin irreversibly inhibits cyclooxygenase, thereby inhibiting TXA2 synthesis.

Clopidogrel, prasugrel, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa via $P2Y_{12}$ receptor.

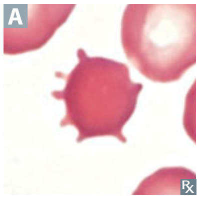
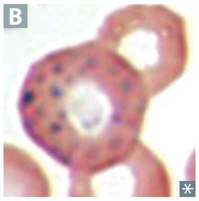
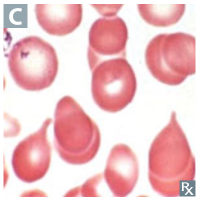
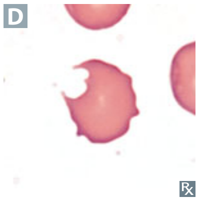
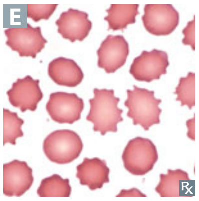
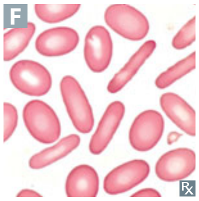
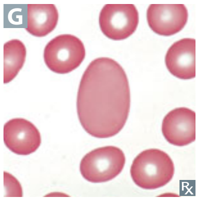
Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly.

Ristocetin activates vWF to bind GpIb. Failure of aggregation with ristocetin assay occurs in von Willebrand disease and Bernard-Soulier syndrome.

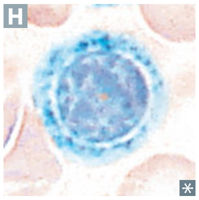
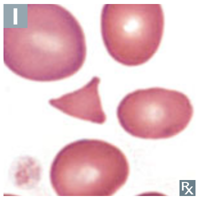
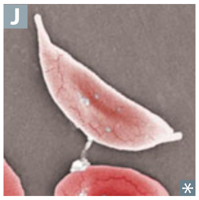
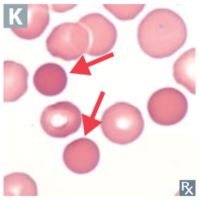
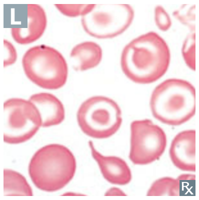

Clopidogrel, prasugrel, ticlopidine
Platelet
Inside platelets
(vWF)
(fibrinogen)
Aspirin
Fibrinogen
COX
Arachidonic acid
TXA_2
$P2Y_{12}$ receptor
4B
4A
GpIIb/IIIa
Deficiency: **Glanzmann thrombasthenia**
GpIIb/IIIa insertion
Abciximab, eptifibatide, tirofiban
Deficiency: **Bernard-Soulier syndrome**
Thrombin-thrombomodulin complex
Protein C
Activated protein C
Vascular endothelial cells
❸
Deficiency: **von Willebrand disease**
Subendothelial collagen
GpIb
vWF
❷
❶
Inside endothelial cells
(vWF + factor VIII)
thromboplastin
tPA, PGI_2

▸ HEMATOLOGY AND ONCOLOGY—PATHOLOGY

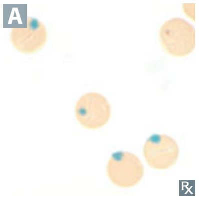
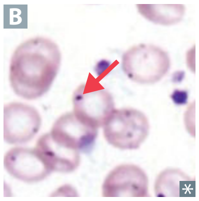
Pathologic RBC forms

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Acanthocyte (“spur cell”) A		Liver disease, abetalipoproteinemia (states of cholesterol dysregulation).	*Acantho* = spiny.
Basophilic stippling B		Lead poisoning, sideroblastic anemias, myelodysplastic syndromes.	Seen primarily in peripheral smear, vs ringed sideroblasts seen in bone marrow. Aggregation of residual ribosomes.
Dacrocyte (“teardrop cell”) C		Bone marrow infiltration (eg, myelofibrosis).	RBC “sheds a tear” because it’s mechanically squeezed out of its home in the bone marrow.
Degmacyte (“bite cell”) D		G6PD deficiency.	
Echinocyte (“burr cell”) E		End-stage renal disease, liver disease, pyruvate kinase deficiency.	Different from acanthocyte; its projections are more uniform and smaller.
Elliptocyte F		Hereditary elliptocytosis, usually asymptomatic; caused by mutation in genes encoding RBC membrane proteins (eg, spectrin).	
Macro-ovalocyte G		Megaloblastic anemia (also hypersegmented PMNs).	

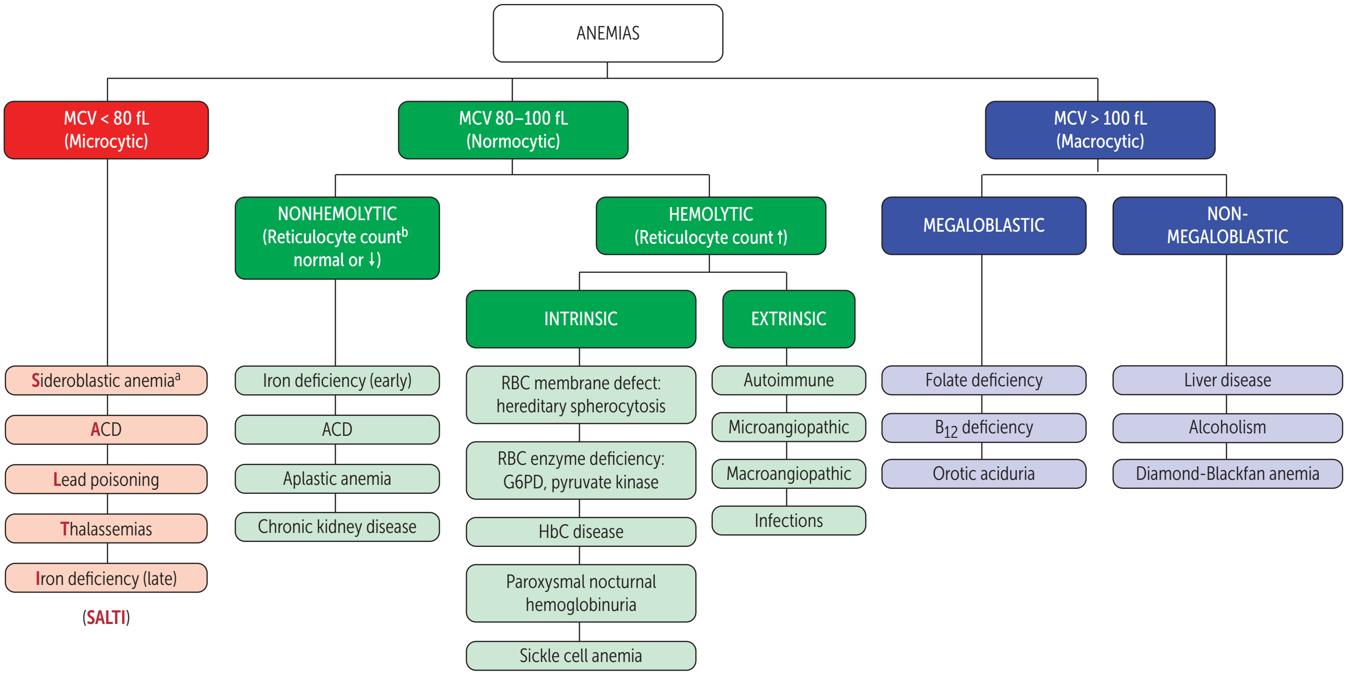
Pathologic RBC forms *(continued)*

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Ringed sideroblast H		Sideroblastic anemia. Excess iron in mitochondria.	Seen in bone marrow, vs basophilic stippling in peripheral smear.
Schistocyte I		Microangiopathic hemolytic anemias, including DIC, TTP/HUS, HELLP syndrome, mechanical hemolysis (eg, heart valve prosthesis).	Fragmented RBCs. Examples include helmet cell.
Sickle cell J		Sickle cell anemia.	Sickling occurs with dehydration, deoxygenation, and at high altitude.
Spherocyte K		Hereditary spherocytosis, drug- and infection-induced hemolytic anemia.	
Target cell L		HbC disease, Asplenia, Liver disease, Thalassemia.	"HALT," said the hunter to his target.

Other RBC abnormalities

TYPE	EXAMPLE	ASSOCIATED PATHOLOGY	NOTES
Heinz bodies A		Seen in G6PD deficiency.	Oxidation of Hb -SH groups to -S—S- → Hb precipitation (Heinz bodies), with subsequent phagocytic damage to RBC membrane → bite cells.
Howell-Jolly bodies B		Seen in patients with functional hyposplenia or asplenia.	Basophilic nuclear remnants found in RBCs. Howell-Jolly bodies are normally removed from RBCs by splenic macrophages.

Anemias


ANEMIAS
MCV < 80 fL (Microcytic)
MCV 80–100 fL (Normocytic)
MCV > 100 fL (Macrocytic)
Sideroblastic anemia[a]
ACD
Lead poisoning
Thalassemias
Iron deficiency (late)
(SALTI)
NONHEMOLYTIC (Reticulocyte count[b] normal or ↓)
Iron deficiency (early)
ACD
Aplastic anemia
Chronic kidney disease
HEMOLYTIC (Reticulocyte count ↑)
INTRINSIC
RBC membrane defect: hereditary spherocytosis
RBC enzyme deficiency: G6PD, pyruvate kinase
HbC disease
Paroxysmal nocturnal hemoglobinuria
Sickle cell anemia
EXTRINSIC
Autoimmune
Microangiopathic
Macroangiopathic
Infections
MEGALOBLASTIC
Folate deficiency
B12 deficiency
Orotic aciduria
NON-MEGALOBLASTIC
Liver disease
Alcoholism
Diamond-Blackfan anemia

On a peripheral blood smear, a lymphocyte nucleus is approximately the same size as a normocytic RBC. If RBC is larger than lymphocyte nucleus, consider macrocytosis; if RBC is smaller, consider microcytosis.

[a] Copper deficiency can cause a microcytic sideroblastic anemia.

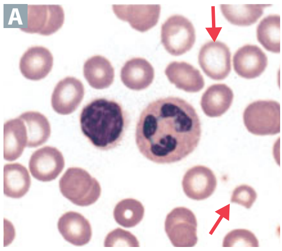
[b] Corrected reticulocyte count (% reticulocytes × [patient hematocrit/normal hematocrit]) is used to determine if bone marrow response is adequate (> 2%).

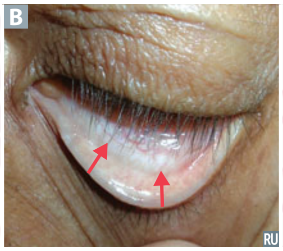
Microcytic (MCV < 80 fL), hypochromic anemia

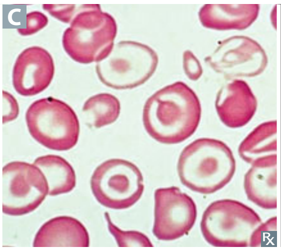
Iron deficiency	↓ iron due to chronic bleeding (eg, GI loss, menorrhagia), malnutrition, absorption disorders, GI surgery (eg, gastrectomy), or ↑ demand (eg, pregnancy) → ↓ final step in heme synthesis. Labs: ↓ iron, ↑ TIBC, ↓ ferritin, ↑ free erythrocyte protoporphyrin. Microcytosis and hypochromasia (central pallor) **A**. Symptoms: fatigue, conjunctival pallor **B**, pica (consumption of nonfood substances), spoon nails (koilonychia). May manifest as glossitis, cheilosis, Plummer-Vinson syndrome (triad of iron deficiency anemia, esophageal webs, and dysphagia).
α-thalassemia	Defect: α-globin gene deletions → ↓ α-globin synthesis. *cis* deletion (both deletions occur on same chromosome) prevalent in Asian populations; *trans* deletion (deletions occur on separate chromosomes) prevalent in African populations. 4 allele deletion: no α-globin. Excess γ-globin forms γ_4 (Hb Barts). Incompatible with life (causes hydrops fetalis). 3 allele deletion: inheritance of chromosome with *cis* deletion + a chromosome with 1 allele deleted → HbH disease. Very little α-globin. Excess β-globin forms β_4 (HbH). 2 allele deletion: less clinically severe anemia. 1 allele deletion: no anemia (clinically silent).

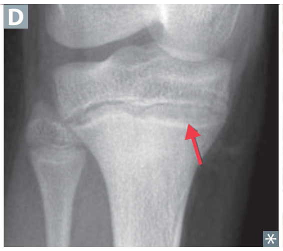
Microcytic (MCV < 80 fL), hypochromic anemia *(continued)*

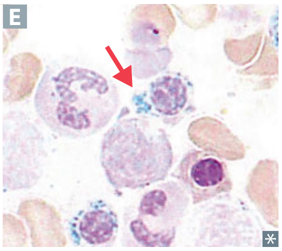
β-thalassemia	Point mutations in splice sites and promoter sequences → ↓ β-globin synthesis. Prevalent in Mediterranean populations. β-thalassemia minor (heterozygote): β chain is underproduced. Usually asymptomatic. Diagnosis confirmed by ↑ HbA_2 (> 3.5%) on electrophoresis. β-thalassemia major (homozygote): β chain is absent → severe microcytic, hypochromic anemia with target cells and increased anisopoikilocytosis C requiring blood transfusion (2° hemochromatosis). Marrow expansion ("crew cut" on skull x-ray) → skeletal deformities. "Chipmunk" facies. Extramedullary hematopoiesis → hepatosplenomegaly. ↑ risk of parvovirus B19–induced aplastic crisis. ↑ HbF ($\alpha_2\gamma_2$). HbF is protective in the infant and disease becomes symptomatic only after 6 months, when fetal hemoglobin declines. HbS/β-thalassemia heterozygote: mild to moderate sickle cell disease depending on amount of β-globin production.
Lead poisoning	Lead inhibits ferrochelatase and ALA dehydratase → ↓ heme synthesis and ↑ RBC protoporphyrin. Also inhibits rRNA degradation → RBCs retain aggregates of rRNA (basophilic stippling). Symptoms of **LEAD** poisoning: - **L**ead **L**ines on gingivae (Burton lines) and on metaphyses of long bones D on x-ray. - **E**ncephalopathy and **E**rythrocyte basophilic stippling. - **A**bdominal colic and sideroblastic **A**nemia. - **D**rops—wrist and foot drop. **D**imercaprol and E**D**TA are 1st line of treatment. **Succ**imer used for chelation for kids (It "**suc**ks" to be a kid who eats lead). Exposure risk ↑ in old houses with chipped paint.
Sideroblastic anemia	Causes: genetic (eg, X-linked defect in ALA synthase gene), acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead, vitamin B_6 deficiency, copper deficiency, isoniazid). Lab findings: ↑ iron, normal/↓ TIBC, ↑ ferritin. Ringed sideroblasts (with iron-laden, Prussian blue–stained mitochondria) seen in bone marrow E. Peripheral blood smear: basophilic stippling of RBCs. Treatment: pyridoxine (B_6, cofactor for ALA synthase).



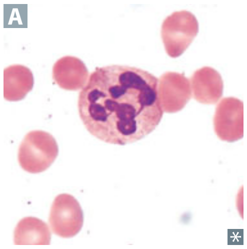






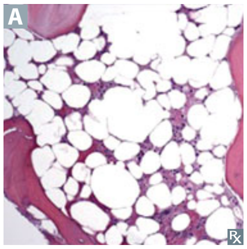


Macrocytic (MCV > 100 fL) anemia

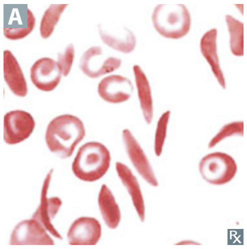
	DESCRIPTION	FINDINGS
Megaloblastic anemia 	Impaired DNA synthesis → maturation of nucleus of precursor cells in bone marrow delayed relative to maturation of cytoplasm.	RBC macrocytosis, hypersegmented neutrophils A, glossitis.
Folate deficiency	Causes: malnutrition (eg, alcoholics), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), ↑ requirement (eg, hemolytic anemia, pregnancy).	↑ homocysteine, normal methylmalonic acid. **No neurologic symptoms** (vs B_{12} deficiency).
Vitamin B_{12} (cobalamin) deficiency	Causes: insufficient intake (eg, veganism), malabsorption (eg, Crohn disease), pernicious anemia, *Diphyllobothrium latum* (fish tapeworm), gastrectomy.	↑ homocysteine, ↑ methylmalonic acid. **Neurologic symptoms:** reversible dementia, subacute combined degeneration (due to involvement of B_{12} in fatty acid pathways and myelin synthesis): spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction. Historically diagnosed with the Schilling test, a 4-stage test that determines if the cause is dietary insufficiency vs malabsorption. Anemia 2° to insufficient intake may take several years to develop due to liver's ability to store B_{12} (as opposed to folate deficiency).
Orotic aciduria	Inability to convert orotic acid to UMP (de novo pyrimidine synthesis pathway) because of defect in UMP synthase. Autosomal recessive. Presents in children as failure to thrive, developmental delay, and megaloblastic anemia refractory to folate and B_{12}. No hyperammonemia (vs ornithine transcarbamylase deficiency—↑ orotic acid with hyperammonemia).	Orotic acid in urine. Treatment: uridine monophosphate to bypass mutated enzyme.
Nonmegaloblastic anemia	Macrocytic anemia in which DNA synthesis is unimpaired. Causes: alcoholism, liver disease.	RBC macrocytosis without hypersegmented neutrophils.
Diamond-Blackfan anemia	Rapid-onset anemia within 1st year of life due to intrinsic defect in erythroid progenitor cells.	↑ % HbF (but ↓ total Hb). Short stature, craniofacial abnormalities, and upper extremity malformations (triphalangeal thumbs) in up to 50% of cases.

Normocytic, normochromic anemia	Normocytic, normochromic anemias are classified as nonhemolytic or hemolytic. The hemolytic anemias are further classified according to the cause of the hemolysis (intrinsic vs extrinsic to the RBC) and by the location of the hemolysis (intravascular vs extravascular). Hemolysis can lead to increases in LDH, reticulocytes, unconjugated bilirubin, urobilinogen in urine.
Intravascular hemolysis	Findings: ↓ haptoglobin, ↑ schistocytes on blood smear. Characteristic hemoglobinuria, hemosiderinuria, and urobilinogen in urine. May also see ↑ unconjugated bilirubin. Notable causes are mechanical hemolysis (eg, prosthetic valve), paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemias.
Extravascular hemolysis	Findings: macrophages in spleen clear RBCs. Spherocytes in peripheral smear (most commonly hereditary spherocytosis and autoimmune hemolytic anemia), no hemoglobinuria/hemosiderinuria. Can present with urobilinogen in urine.

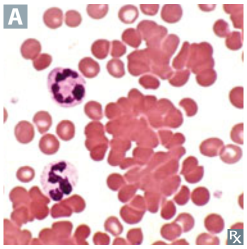
Nonhemolytic, normocytic anemia

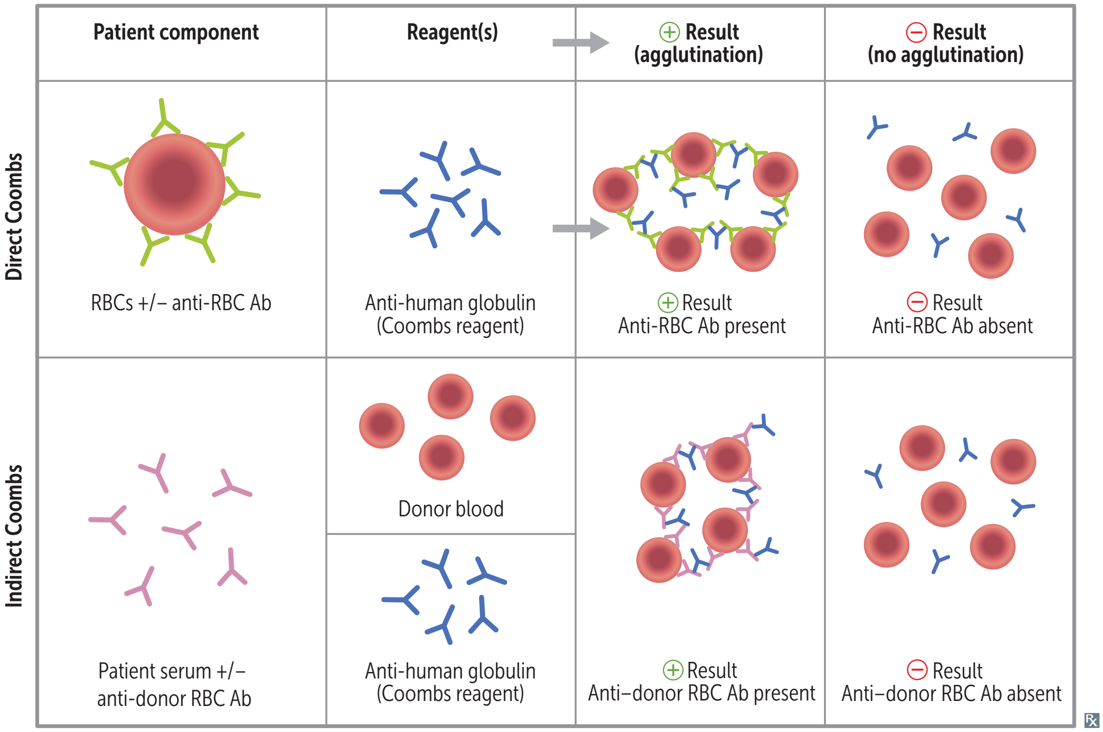
	DESCRIPTION	FINDINGS
Anemia of chronic disease	Inflammation → ↑ hepcidin (released by liver, binds ferroportin on intestinal mucosal cells and macrophages, thus inhibiting iron transport) → ↓ release of iron from macrophages and ↓ iron absorption from gut. Associated with conditions such as rheumatoid arthritis, SLE, neoplastic disorders, and chronic kidney disease.	↓ iron, ↓ TIBC, ↑ ferritin. Normocytic, but can become microcytic. Treatment: address underlying cause of inflammation, judicious use of blood transfusion, consider erythropoiesis-stimulating agents (ESAs) such as EPO (chronic kidney disease only).
Aplastic anemia 	Caused by failure or destruction of myeloid stem cells due to: ▪ Radiation and drugs (benzene, chloramphenicol, alkylating agents, antimetabolites) ▪ Viral agents (parvovirus B19, EBV, HIV, hepatitis viruses) ▪ Fanconi anemia (DNA repair defect causing bone marrow failure; macrocytosis may be seen on CBC); also short stature, ↑ incidence of tumors/leukemia, café-au-lait spots, thumb/radial defects ▪ Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis	↓ reticulocyte count, ↑ EPO. Pancytopenia characterized by severe anemia, leukopenia, and thrombocytopenia. Normal cell morphology, but hypocellular bone marrow with fatty infiltration A (dry bone marrow tap). Symptoms: fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection. Treatment: withdrawal of offending agent, immunosuppressive regimens (eg, antithymocyte globulin, cyclosporine), bone marrow allograft, RBC/platelet transfusion, bone marrow stimulation (eg, GM-CSF).

Intrinsic hemolytic anemia

	DESCRIPTION	FINDINGS
Hereditary spherocytosis	Extravascular hemolysis due to defect in proteins interacting with RBC membrane skeleton and plasma membrane (eg, ankyrin, band 3, protein 4.2, spectrin). Mostly autosomal dominant inheritance. Results in small, round RBCs with less surface area and no central pallor (↑ MCHC) → premature removal by spleen.	Splenomegaly, aplastic crisis (parvovirus B19 infection). Labs: osmotic fragility test ⊕. Normal to ↓ MCV with abundance of cells. Treatment: splenectomy.
G6PD deficiency	Most common enzymatic disorder of RBCs. Causes extravascular and intravascular hemolysis. X-linked recessive. Defect in G6PD → ↓ glutathione → ↑ RBC susceptibility to oxidant stress. Hemolytic anemia following oxidant stress (eg, sulfa drugs, antimalarials, infections, **fava beans**).	Back pain, hemoglobinuria a few days after oxidant **stress**. Labs: blood smear shows RBCs with **Heinz** bodies and **bite** cells. "**Stress** makes me eat **bites** of **fava beans** with **Heinz** ketchup."
Pyruvate kinase deficiency	Autosomal recessive pyruvate kinase defect → ↓ ATP → rigid RBCs → extravascular hemolysis. Increases levels of 2,3-BPG → ↓ hemoglobin affinity for O_2.	Hemolytic anemia in a newborn.
Paroxysmal nocturnal hemoglobinuria	↑ complement-mediated intravascular RBC lysis (impaired synthesis of GPI anchor for decay-accelerating factor that protects RBC membrane from complement). Acquired mutation in a hematopoietic stem cell. ↑ incidence of acute leukemias. Patients may report red or pink urine (from hemoglobinuria).	Associated with aplastic anemia. Triad: Coombs ⊖ hemolytic anemia, pancytopenia, and venous thrombosis. Labs: CD55/59 ⊖ RBCs on flow cytometry. Treatment: eculizumab (terminal complement inhibitor).
Sickle cell anemia A  B 	HbS point mutation causes a single amino acid replacement in β chain (substitution of glutamic acid with valine). Causes extravascular and intravascular hemolysis. Pathogenesis: low O_2, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) → anemia, vaso-occlusive disease. Newborns are initially asymptomatic because of ↑ HbF and ↓ HbS. Heterozygotes (sickle cell trait) also have resistance to malaria. 8% of African Americans carry an HbS allele. Sickle cells are crescent-shaped RBCs A. "Crew cut" on skull x-ray due to marrow expansion from ↑ erythropoiesis (also seen in thalassemias).	Complications in sickle cell disease: ▪ Aplastic crisis (due to parvovirus B19). ▪ Autosplenectomy (Howell-Jolly bodies) → ↑ risk of infection by encapsulated organisms (eg, *S pneumoniae*). ▪ Splenic infarct/sequestration crisis. ▪ *Salmonella* osteomyelitis. ▪ Painful crises (vaso-occlusive): dactylitis B (painful swelling of hands/feet), priapism, acute chest syndrome, avascular necrosis, stroke. ▪ Renal papillary necrosis (↓ Po_2 in papilla) and microhematuria (medullary infarcts). Diagnosis: hemoglobin electrophoresis. Treatment: hydroxyurea (↑ HbF), hydration.
HbC disease	Glutamic acid–to-lyCine (lysine) mutation in β-globin. Causes extravascular hemolysis.	Patients with HbSC (1 of each mutant gene) have milder disease than HbSS patients. Blood smear in homozygotes: hemoglobin Crystals inside RBCs, target cells.

Extrinsic hemolytic anemia

	DESCRIPTION	FINDINGS
Autoimmune hemolytic anemia  	Warm (Ig**G**)—chronic anemia seen in SLE and CLL and with certain drugs (eg, α-methyldopa) ("**warm** weather is **G**reat"). Cold (Ig**M** and complement)—acute anemia triggered by cold; seen in CLL, ***M**ycoplasma pneumoniae* infections, and infectious **M**ononucleosis ("**cold** weather is **MMM**iserable"). RBC agglutinates A may cause painful, blue fingers and toes with cold exposure. Many warm and cold AIHAs are idiopathic in etiology.	Autoimmune hemolytic anemias are usually Coombs ⊕. Direct Coombs test—anti-Ig antibody (Coombs reagent) added to patient's RBCs. RBCs agglutinate if RBCs are coated with Ig. Indirect Coombs test—normal RBCs added to patient's serum. If serum has anti-RBC surface Ig, RBCs agglutinate when Coombs reagent added.


Patient component
Reagent(s)
⊕ Result (agglutination)
⊖ Result (no agglutination)
Direct Coombs
RBCs +/– anti-RBC Ab
Anti-human globulin (Coombs reagent)
⊕ Result Anti-RBC Ab present
⊖ Result Anti-RBC Ab absent
Indirect Coombs
Patient serum +/– anti-donor RBC Ab
Donor blood
Anti-human globulin (Coombs reagent)
⊕ Result Anti–donor RBC Ab present
⊖ Result Anti–donor RBC Ab absent

	DESCRIPTION	FINDINGS
Microangiopathic anemia	Pathogenesis: RBCs are damaged when passing through obstructed or narrowed vessel lumina. Seen in DIC, TTP/HUS, SLE, HELLP syndrome, and malignant hypertension.	**Schisto**cytes (eg, "helmet cells") are seen on peripheral blood smear due to mechanical destruction (***schisto*** = to split) of RBCs.
Macroangiopathic anemia	Prosthetic heart valves and aortic stenosis may also cause hemolytic anemia 2° to mechanical destruction of RBCs.	Schistocytes on peripheral blood smear.
Infections	↑ destruction of RBCs (eg, malaria, *Babesia*).	

Lab values in anemia

	Iron deficiency	Chronic disease	Hemo-chromatosis	Pregnancy/ OCP use
Serum iron	↓	↓	↑	—
Transferrin or TIBC	↑	↓[a]	↓	↑
Ferritin	↓	↑	↑	—
% transferrin saturation (serum iron/TIBC)	↓↓	—	↑↑	↓

↑↓ = 1° disturbance.

Transferrin—transports iron in blood.

TIBC—indirectly measures transferrin.

Ferritin—1° iron storage protein of body.

[a] Evolutionary reasoning—pathogens use circulating iron to thrive. The body has adapted a system in which iron is stored within the cells of the body and prevents pathogens from acquiring circulating iron.

Leukopenias

CELL TYPE	CELL COUNT	CAUSES
Neutropenia	Absolute neutrophil count < 1500 cells/mm^3. Severe infections typical when < 500 cells/mm^3.	Sepsis/postinfection, drugs (including chemotherapy), aplastic anemia, SLE, radiation
Lymphopenia	Absolute lymphocyte count < 1500 cells/mm^3 (< 3000 cells/mm^3 in children)	HIV, DiGeorge syndrome, SCID, SLE, corticosteroids,[a] radiation, sepsis, postoperative
Eosinopenia	Absolute eosinophil count < 30 cells/mm^3	Cushing syndrome, corticosteroids[a]

[a] Corticosteroids cause neutrophilia, despite causing eosinopenia and lymphopenia. Corticosteroids ↓ activation of neutrophil adhesion molecules, impairing migration out of the vasculature to sites of inflammation. In contrast, corticosteroids sequester eosinophils in lymph nodes and cause apoptosis of lymphocytes.

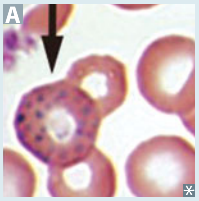
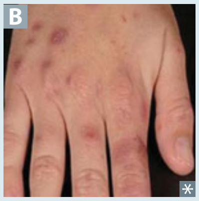
Left shift

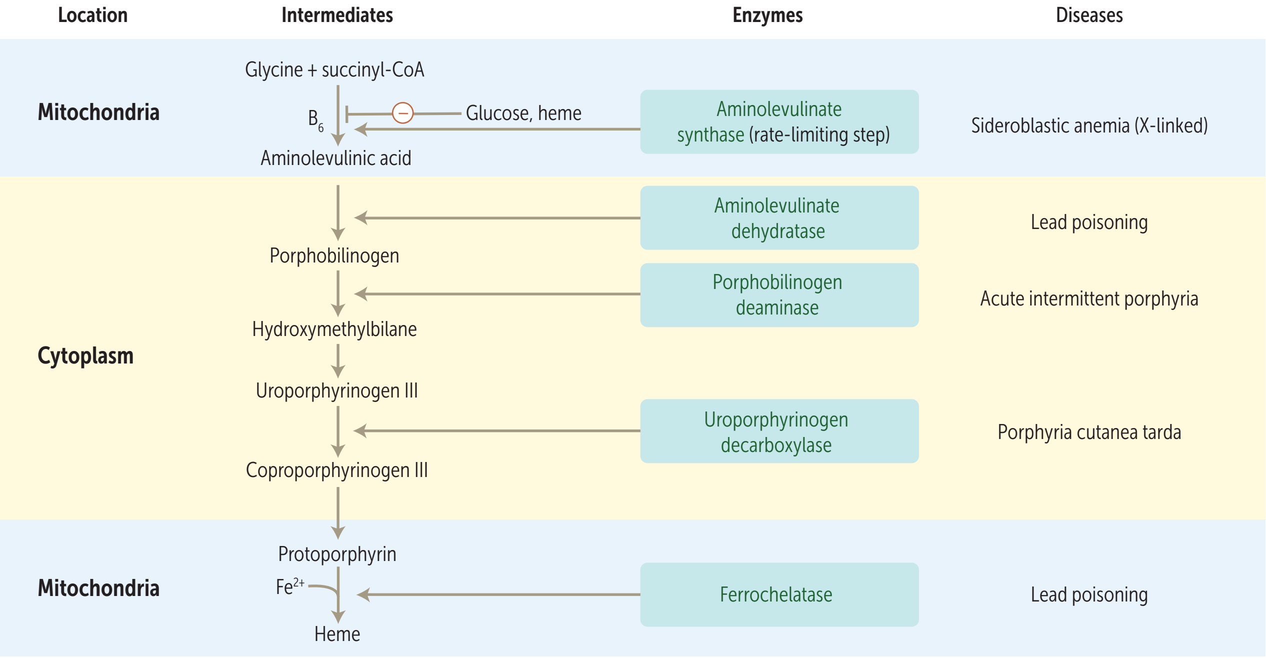
↑ neutrophil precursors, such as band cells and metamyelocytes, in peripheral blood. Usually seen with neutrophilia in the acute response to infection or inflammation. Called leukoerythroblastic reaction when left shift is seen with immature RBCs. Occurs with severe anemia (physiologic response) or marrow response (eg, fibrosis, tumor taking up space in marrow).

A left shift is a shift to a more immature cell in the maturation process.

Heme synthesis, porphyrias, and lead poisoning

The porphyrias are hereditary or acquired conditions of defective heme synthesis that lead to the accumulation of heme precursors. Lead inhibits specific enzymes needed in heme synthesis, leading to a similar condition.

CONDITION	AFFECTED ENZYME	ACCUMULATED SUBSTRATE	PRESENTING SYMPTOMS
Lead poisoning  	Ferrochelatase and ALA dehydratase	Protoporphyrin, ALA (blood)	Microcytic anemia (basophilic stippling in peripheral smear **A**, ringed sideroblasts in bone marrow), GI and kidney disease. Children—exposure to lead paint → mental deterioration. Adults—environmental exposure (eg, batteries, ammunition) → headache, memory loss, demyelination.
Acute intermittent porphyria	Porphobilinogen deaminase, previously known as uroporphyrinogen I synthase (autosomal dominant mutation)	Porphobilinogen, ALA	Symptoms (**5 P's**): - **P**ainful abdomen - **P**ort wine–colored urine - **P**olyneuropathy - **P**sychological disturbances - **P**recipitated by drugs (eg, cytochrome P-450 inducers), alcohol, starvation Treatment: glucose and heme, which inhibit ALA synthase.
Porphyria cutanea tarda  	Uroporphyrinogen decarboxylase (autosomal dominant mutation)	Uroporphyrin (tea-colored urine)	Blistering cutaneous photosensitivity and hyperpigmentation **B**. Most common porphyria. Exacerbated with alcohol consumption.


Location
Intermediates
Enzymes
Diseases
Mitochondria
Glycine + succinyl-CoA
B_6
Glucose, heme
Aminolevulinic acid
Aminolevulinate synthase (rate-limiting step)
Sideroblastic anemia (X-linked)
Cytoplasm
Aminolevulinate dehydratase
Lead poisoning
Porphobilinogen
Porphobilinogen deaminase
Acute intermittent porphyria
Hydroxymethylbilane
Uroporphyrinogen III
Uroporphyrinogen decarboxylase
Porphyria cutanea tarda
Coproporphyrinogen III
Mitochondria
Protoporphyrin
Fe^{2+}
Ferrochelatase
Lead poisoning
Heme

↓ heme → ↑ ALA synthase activity
↑ heme → ↓ ALA synthase activity

Iron poisoning	High mortality rate with accidental ingestion by children (adult iron tablets may look like candy).
MECHANISM	Cell death due to peroxidation of membrane lipids.
SYMPTOMS/SIGNS	Nausea, vomiting, gastric bleeding, lethargy, scarring leading to GI obstruction.
TREATMENT	Chelation (eg, IV deferoxamine, oral deferasirox) and dialysis.

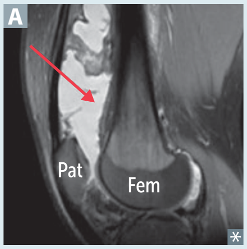
Coagulation disorders

PT—tests function of common and extrinsic pathway (factors I, II, V, VII, and X). Defect → ↑ PT.

INR (international normalized ratio)—calculated from PT. 1 = normal, > 1 = prolonged. Most common test used to follow patients on warfarin.

PTT—tests function of common and intrinsic pathway (all factors except VII and XIII). Defect → ↑ PTT.

Coagulation disorders can be due to clotting factor deficiencies or acquired inhibitors. Diagnosed with a mixing study, in which normal plasma is added to patient's plasma. Clotting factor deficiencies should correct (the PT or PTT returns to within the appropriate normal range), whereas factor inhibitors will not correct.

DISORDER	PT	PTT	MECHANISM AND COMMENTS
Hemophilia A, B, or C  	—	↑	Intrinsic pathway coagulation defect. ▪ A: deficiency of factor VIII → ↑ PTT; X-linked recessive. ▪ B: deficiency of factor IX → ↑ PTT; X-linked recessive. ▪ C: deficiency of factor XI → ↑ PTT; autosomal recessive. Macrohemorrhage in hemophilia—hemarthroses (bleeding into joints, such as knee A), easy bruising, bleeding after trauma or surgery (eg, dental procedures). Treatment: desmopressin + factor VIII concentrate (A); factor IX concentrate (B); factor XI concentrate (C).
Vitamin K deficiency	↑	↑	General coagulation defect. Bleeding time normal. ↓ activity of factors II, VII, IX, X, protein C, protein S.

Platelet disorders

Defects in platelet plug formation → ↑ bleeding time (BT).
Platelet abnormalities → microhemorrhage: mucous membrane bleeding, epistaxis, petechiae, purpura, ↑ bleeding time, possibly decreased platelet count (PC).

DISORDER	PC	BT	MECHANISM AND COMMENTS
Bernard-Soulier syndrome	–/↓	↑	Defect in platelet plug formation. Large platelets. ↓ GpIb → defect in platelet-to-vWF adhesion.
Glanzmann thrombasthenia	–	↑	Defect in platelet integrin $\alpha_{IIb}\beta_3$ (GpIIb/IIIa) → defect in platelet-to-platelet aggregation, and therefore platelet plug formation. Labs: blood smear shows no platelet clumping.
Hemolytic-uremic syndrome	↓	↑	Characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure. Typical HUS is seen in children, accompanied by diarrhea and commonly caused by enterohemorrhagic *E coli* (EHEC) (eg, O157:H7). HUS in adults does not present with diarrhea; EHEC infection not required. Same spectrum as TTP, with a similar clinical presentation and same initial treatment of plasmapheresis.
Immune thrombocytopenia	↓	↑	Anti-GpIIb/IIIa antibodies → splenic macrophage consumption of platelet-antibody complex. May be 1° (idiopathic) or 2° to autoimmune disorder, viral illness, malignancy, or drug reaction. Labs: ↑ megakaryocytes on bone marrow biopsy. Treatment: steroids, IVIG, splenectomy (for refractory ITP).
Thrombotic thrombocytopenic purpura	↓	↑	Inhibition or deficiency of ADAMTS 13 (vWF metalloprotease) → ↓ degradation of vWF multimers. Pathogenesis: ↑ large vWF multimers → ↑ platelet adhesion → ↑ platelet aggregation and thrombosis. Labs: schistocytes, ↑ LDH, normal coagulation parameters. Symptoms: pentad of neurologic and renal symptoms, fever, thrombocytopenia, and microangiopathic hemolytic anemia. Treatment: plasmapheresis, steroids.

Mixed platelet and coagulation disorders

DISORDER	PC	BT	PT	PTT	MECHANISM AND COMMENTS
von Willebrand disease	—	↑	—	—/↑	Intrinsic pathway coagulation defect: ↓ vWF → ↑ PTT (vWF acts to carry/protect factor VIII). Defect in platelet plug formation: ↓ vWF → defect in platelet-to-vWF adhesion. Autosomal dominant. Mild but most common inherited bleeding disorder. No platelet aggregation with ristocetin cofactor assay. Treatment: desmopressin, which releases vWF stored in endothelium.
Disseminated intravascular coagulation	↓	↑	↑	↑	Widespread activation of clotting → deficiency in clotting factors → bleeding state. Causes: **S**epsis (gram ⊖), **T**rauma, **O**bstetric complications, acute **P**ancreatitis, **M**alignancy, **N**ephrotic syndrome, **T**ransfusion (**STOP M**aking **N**ew **T**hrombi). Labs: schistocytes, ↑ fibrin degradation products (D-dimers), ↓ fibrinogen, ↓ factors V and VIII.

Hereditary thrombosis syndromes leading to hypercoagulability

DISEASE	DESCRIPTION
Antithrombin deficiency	Inherited deficiency of antithrombin: has no direct effect on the PT, PTT, or thrombin time but diminishes the increase in PTT following heparin administration. Can also be acquired: renal failure/nephrotic syndrome → antithrombin loss in urine → ↓ inhibition of factors IIa and Xa.
Factor V Leiden	Production of mutant factor V (G → A DNA point mutation → Arg506Gln mutation near the cleavage site) that is resistant to degradation by activated protein C. Most common cause of inherited hypercoagulability in Caucasians. Complications include DVT, cerebral vein thromboses, recurrent pregnancy loss.
Protein C or S deficiency	↓ ability to inactivate factors Va and VIIIa. ↑ risk of thrombotic skin necrosis with hemorrhage after administration of warfarin. If this occurs, think protein C deficiency. Together, protein **C C**ancels, and protein **S S**tops, coagulation.
Prothrombin gene mutation	Mutation in 3′ untranslated region → ↑ production of prothrombin → ↑ plasma levels and venous clots.

Blood transfusion therapy

COMPONENT	DOSAGE EFFECT	CLINICAL USE
Packed RBCs	↑ Hb and O_2 carrying capacity	Acute blood loss, severe anemia
Platelets	↑ platelet count (↑ ~ $5000/mm^3$/unit)	Stop significant bleeding (thrombocytopenia, qualitative platelet defects)
Fresh frozen plasma/ prothrombin complex concentrate	↑ coagulation factor levels	DIC, cirrhosis, immediate anticoagulation reversal
Cryoprecipitate	Contains fibrinogen, factor VIII, factor XIII, vWF, and fibronectin	Coagulation factor deficiencies involving fibrinogen and factor VIII

Blood transfusion risks include infection transmission (low), transfusion reactions, iron overload (may lead to 2° hemochromatosis), hypocalcemia (citrate is a Ca^{2+} chelator), and hyperkalemia (RBCs may lyse in old blood units).

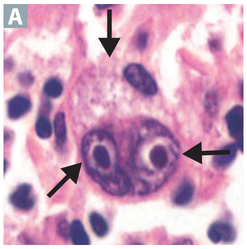
Leukemia vs lymphoma

Leukemia	Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood.
Lymphoma	Discrete tumor mass arising from lymph nodes. Presentations often blur definitions.

Hodgkin vs non-Hodgkin lymphoma

Hodgkin	Non-Hodgkin
Both may present with constitutional ("B") signs/symptoms: low-grade fever, night sweats, weight loss (patients are **B**othered by **B** symptoms).	
Localized, single group of nodes; contiguous spread (stage is strongest predictor of prognosis). Overall prognosis better than that of non-Hodgkin lymphoma.	Multiple lymph nodes involved; extranodal involvement common; noncontiguous spread.
Characterized by Reed-Sternberg cells.	Majority involve B cells; a few are of T-cell lineage.
Bimodal distribution–young adulthood and > 55 years; more common in men except for nodular sclerosing type.	Can occur in children and adults.
Associated with EBV.	May be associated with HIV and autoimmune diseases.

Hodgkin lymphoma

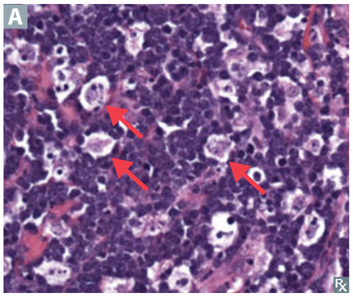


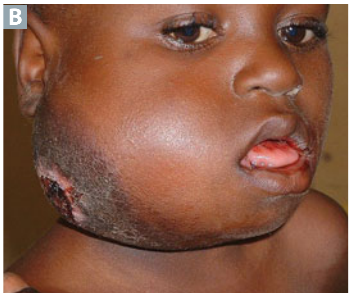
Contains Reed-Sternberg cells: distinctive tumor giant cells; binucleate or bilobed with the 2 halves as mirror images ("owl eyes" A). 2 owl eyes × 15 = 30. RS cells are CD15+ and CD30+ B-cell origin. Necessary but not sufficient for a diagnosis of Hodgkin lymphoma.

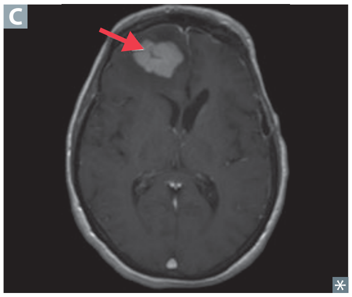
SUBTYPE	NOTES
Nodular sclerosis	Most common
Lymphocyte rich	Best prognosis
Mixed cellularity	Eosinophilia, seen in immunocompromised patients
Lymphocyte depleted	Seen in immunocompromised patients

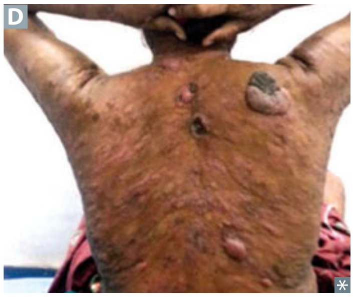
Non-Hodgkin lymphoma

TYPE	OCCURS IN	GENETICS	COMMENTS
Neoplasms of mature B cells			
Burkitt lymphoma	Adolescents or young adults	t(8;14)—translocation of c-*myc* (8) and heavy-chain Ig (14)	"Starry sky" appearance, sheets of lymphocytes with interspersed "tingible body" macrophages (arrows in A). Associated with EBV. Jaw lesion B in endemic form in Africa; pelvis or abdomen in sporadic form.
Diffuse large B-cell lymphoma	Usually older adults, but 20% in children	Alterations in Bcl-2, Bcl-6	Most common type of non-Hodgkin lymphoma in adults.
Follicular lymphoma	Adults	t(14;18)—translocation of heavy-chain Ig (14) and *BCL-2* (18)	Indolent course; Bcl-2 inhibits apoptosis. Presents with painless "waxing and waning" lymphadenopathy. Follicular architecture: small cleaved cells (grade 1), large cells (grade 3), or mixture (grade 2).
Mantle cell lymphoma	Adult males	t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14), CD 5+	Very aggressive, patients typically present with late-stage disease.
Marginal zone lymphoma	Adults	t(11,18)	Associated with chronic inflammation (eg, Sjögren syndrome, chronic gastritis [MALT lymphoma]).
Primary central nervous system lymphoma	Adults	Most commonly associated with HIV/AIDS; pathogenesis involves EBV infection	Considered an AIDS-defining illness. Variable presentation: confusion, memory loss, seizures. Mass lesion(s) on MRI C, needs to be distinguished from toxoplasmosis via CSF analysis or other lab tests.
Neoplasms of mature T cells			
Adult T-cell lymphoma	Adults	Caused by HTLV (associated with IV drug abuse)	Adults present with cutaneous lesions; common in Japan, West Africa, and the Caribbean. Lytic bone lesions, hypercalcemia.
Mycosis fungoides/ Sézary syndrome	Adults		Mycosis fungoides: skin patches D/plaques (cutaneous T-cell lymphoma), characterized by atypical CD4+ cells with "cerebriform" nuclei and intraepidermal neoplastic cell aggregates (Pautrier microabscess). May progress to Sézary syndrome (T-cell leukemia).

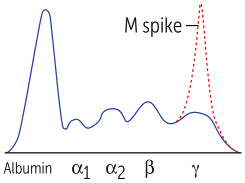








Multiple myeloma



Monoclonal plasma cell ("fried egg" appearance) cancer that arises in the marrow and produces large amounts of IgG (55%) or IgA (25%). Bone marrow > 10% monoclonal plasma cells. Most common 1° tumor arising within bone in people > 40–50 years old.

Associated with:

- ↑ susceptibility to infection
- Primary amyloidosis (AL)
- Punched-out lytic bone lesions on x-ray **A**
- M spike on serum protein electrophoresis
- Ig light chains in urine (Bence Jones protein)
- Rouleaux formation **B** (RBCs stacked like poker chips in blood smear)

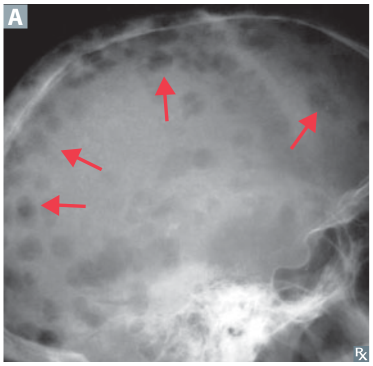
Numerous plasma cells **C** with "clock-face" chromatin and intracytoplasmic inclusions containing immunoglobulin.

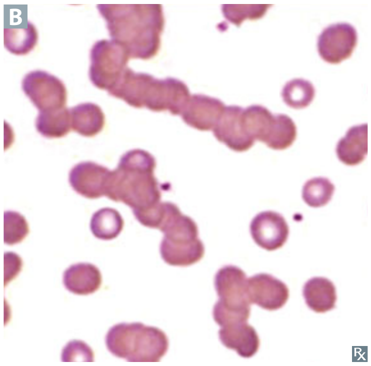
Monoclonal gammopathy of undetermined significance (MGUS)—monoclonal expansion of plasma cells (bone marrow < 10% monoclonal plasma cells), asymptomatic, may lead to multiple myeloma. No "**CRAB**" findings. Patients with MGUS develop multiple myeloma at a rate of 1–2% per year.

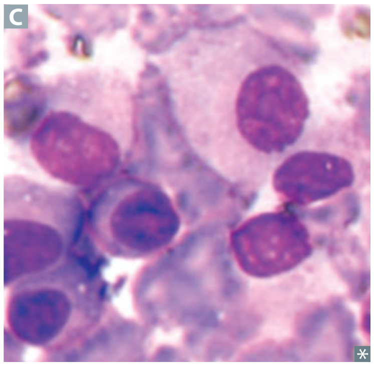
Think **CRAB**:
Hyper**C**alcemia
Renal involvement
Anemia
Bone lytic lesions/**B**ack pain

Multiple **M**yeloma: **M**onoclonal **M** protein spike

Distinguish from **Waldenström macroglobulinemia** → M spike = IgM → hyperviscosity syndrome (eg, blurred vision, Raynaud phenomenon); no "**CRAB**" findings.







Myelodysplastic syndromes

Stem-cell disorders involving ineffective hematopoiesis → defects in cell maturation of nonlymphoid lineages. Caused by de novo mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML.

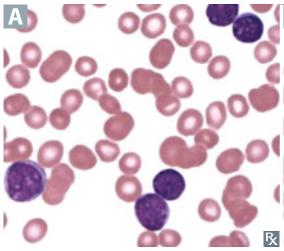
Pseudo–Pelger-Huet anomaly—neutrophils with bilobed nuclei. Typically seen after chemotherapy.

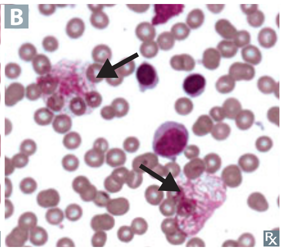
Leukemias

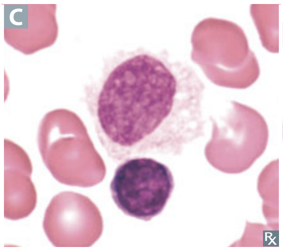
Unregulated growth and differentiation of WBCs in bone marrow → marrow failure → anemia (↓ RBCs), infections (↓ mature WBCs), and hemorrhage (↓ platelets). Usually presents with ↑ circulating WBCs (malignant leukocytes in blood); rare cases present with normal/↓ WBCs.

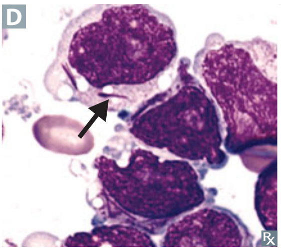
Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

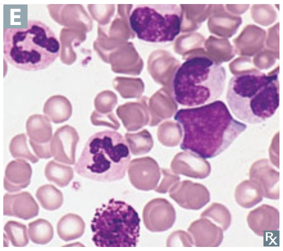
TYPE	NOTES
Lymphoid neoplasms	
Acute lymphoblastic leukemia/lymphoma	Most frequently occurs in children; less common in adults (worse prognosis). T-cell ALL can present as mediastinal mass (presenting as SVC-like syndrome). Associated with Down syndrome. Peripheral blood and bone marrow have ↑↑↑ lymphoblasts A. TdT+ (marker of pre-T and pre-B cells), CD10+ (marker of pre-B cells). Most responsive to therapy. May spread to CNS and testes. t(12;21) → better prognosis.
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Age: > 60 years. Most common adult leukemia. CD20+, CD23+, CD5+ B-cell neoplasm. Often asymptomatic, progresses slowly; smudge cells B in peripheral blood smear; autoimmune hemolytic anemia. CLL = Crushed Little Lymphocytes (smudge cells). Richter transformation—CLL/SLL transformation into an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).
Hairy cell leukemia	Age: Adult males. Mature B-cell tumor. Cells have filamentous, hair-like projections (fuzzy appearing on LM C). Peripheral lymphadenopathy is uncommon. Causes marrow fibrosis → dry tap on aspiration. Patients usually present with massive splenomegaly and pancytopenia. Stains TRAP (tartrate-resistant acid phosphatase) ⊕. TRAP stain largely replaced with flow cytometry. Treatment: cladribine, pentostatin.
Myeloid neoplasms	
Acute myelogenous leukemia	Median onset 65 years. Auer rods D; myeloperoxidase ⊕ cytoplasmic inclusions seen mostly in APL (formerly M3 AML); ↑↑↑ circulating myeloblasts on peripheral smear; adults. Risk factors: prior exposure to alkylating chemotherapy, radiation, myeloproliferative disorders, Down syndrome. APL: t(15;17), responds to all-*trans* retinoic acid (vitamin A), inducing differentiation of promyelocytes; DIC is a common presentation.
Chronic myelogenous leukemia	Occurs across the age spectrum with peak incidence 45–85 years, median age at diagnosis 64 years. Defined by the Philadelphia chromosome (t[9;22], *BCR-ABL*) and myeloid stem cell proliferation. Presents with dysregulated production of mature and maturing granulocytes (eg, neutrophils, metamyelocytes, myelocytes, basophils E) and splenomegaly. May accelerate and transform to AML or ALL ("blast crisis"). Very low LAP as a result of low activity in malignant neutrophils (vs benign neutrophilia [leukemoid reaction], in which LAP is ↑). Responds to *bcr-abl* tyrosine kinase inhibitors (eg, imatinib).











Chronic myeloproliferative disorders

The myeloproliferative disorders (polycythemia vera, essential thrombocythemia, myelofibrosis, and CML) are malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines. Associated with V617F *JAK2* mutation.

Polycythemia vera

Primary polycythemia. Disorder of ↑ RBCs. May present as intense itching after hot shower. Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities A.

↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO).

Treatment: phlebotomy, hydroxyurea, ruxolitinib (JAK1/2 inhibitor).

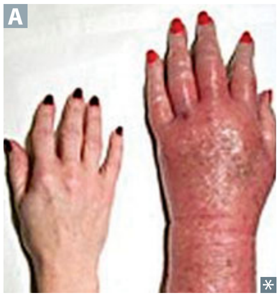
Essential thrombocythemia

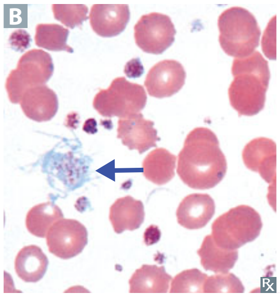
Characterized by massive proliferation of megakaryocytes and platelets. Symptoms include bleeding and thrombosis. Blood smear shows markedly increased number of platelets, which may be large or otherwise abnormally formed B. Erythromelalgia may occur.

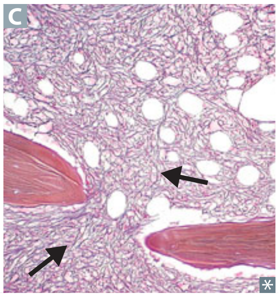
Myelofibrosis

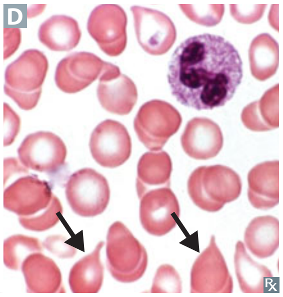
Obliteration of bone marrow with fibrosis C due to ↑ fibroblast activity. Often associated with massive splenomegaly and "**teardrop**" RBCs D. "Bone marrow is **crying** because it's fibrosed and is a dry tap."

	RBCs	WBCs	PLATELETS	PHILADELPHIA CHROMOSOME	*JAK2* MUTATIONS
Polycythemia vera	↑	↑	↑	⊖	⊕
Essential thrombocythemia	–	–	↑	⊖	⊕ (30–50%)
Myelofibrosis	↓	Variable	Variable	⊖	⊕ (30–50%)
CML	↓	↑	↑	⊕	⊖









Polycythemia

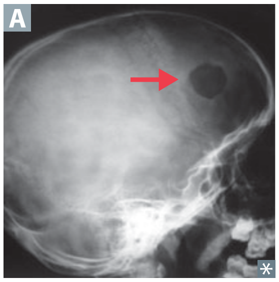
	PLASMA VOLUME	RBC MASS	O_2 SATURATION	EPO LEVELS	ASSOCIATIONS
Relative	↓	–	–	–	Dehydration, burns.
Appropriate absolute	–	↑	↓	↑	Lung disease, congenital heart disease, high altitude.
Inappropriate absolute	–	↑	–	↑	Malignancy (eg, renal cell carcinoma, hepatocellular carcinoma), hydronephrosis. Due to ectopic EPO secretion.
Polycythemia vera	↑	↑↑	–	↓	EPO ↓ in PCV due to negative feedback suppressing renal EPO production.

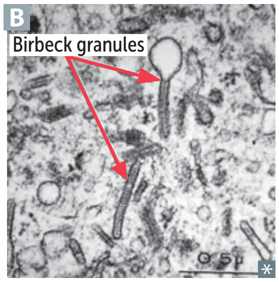
Chromosomal translocations

TRANSLOCATION	ASSOCIATED DISORDER	
t(8;14)	Burkitt lymphoma (c-*myc* activation)	
t(9;22) (**Philadelphia** chromosome)	**CML** (*BCR-ABL* hybrid), ALL (less common, poor prognostic factor)	**Philadelphia** **Crea****ML** cheese. The Ig heavy chain genes on chromosome 14 are constitutively expressed. When other genes (eg, *c-myc* and *BCL-2*) are translocated next to this heavy chain gene region, they are overexpressed.
t(11;14)	Mantle cell lymphoma (cyclin D1 activation)	
t(14;18)	Follicular lymphoma (*BCL-2* activation)	
t(15;17)	APL (M3 type of AML)	Responds to all-*trans* retinoic acid.

Langerhans cell histiocytosis

Collective group of proliferative disorders of dendritic (Langerhans) cells. Presents in a child as lytic bone lesions A and skin rash or as recurrent otitis media with a mass involving the mastoid bone. Cells are functionally immature and do not effectively stimulate primary T cells via antigen presentation. Cells express S-100 (mesodermal origin) and CD1a. Birbeck granules (“tennis rackets” or rod shaped on EM) are characteristic B.





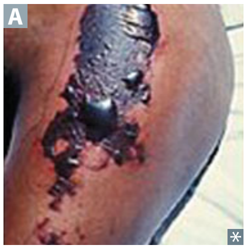
▶ HEMATOLOGY AND ONCOLOGY—PHARMACOLOGY

Heparin

MECHANISM	Lowers the activity of thrombin and factor Xa. Short half-life.
CLINICAL USE	Immediate anticoagulation for pulmonary embolism (PE), acute coronary syndrome, MI, deep venous thrombosis (DVT). Used during pregnancy (does not cross placenta). Follow PTT.
ADVERSE EFFECTS	Bleeding, thrombocytopenia (HIT), osteoporosis, drug-drug interactions. For rapid reversal (antidote), use protamine sulfate (positively charged molecule that binds negatively charged heparin).
NOTES	Low-molecular-weight heparins (eg, enoxaparin, dalteparin) act predominantly on factor Xa. Fondaparinux acts only on factor Xa. Have better bioavailability and 2–4× longer half life than unfractionated heparin; can have better bioavailability, and 2–4 times longer half life; can be administered subcutaneously and without laboratory monitoring. Not easily reversible. **Heparin-induced thrombocytopenia** (HIT)—development of IgG antibodies against heparin-bound platelet factor 4 (PF4). Antibody-heparin-PF4 complex activates platelets → thrombosis and thrombocytopenia.

Direct thrombin inhibitors	Bivalirudin (related to hirudin, the anticoagulant used by leeches), argatroban, dabigatran (only oral agent in class).
MECHANISM	Directly inhibits activity of free and clot-associated thrombin.
CLINICAL USE	Venous thromboembolism, atrial fibrillation. Can be used in HIT. Does not require lab monitoring.
ADVERSE EFFECTS	Bleeding; can reverse dabigatran with idarucizumab. Consider PCC and/or antifibrinolytics (eg, tranexamic acid) if no reversal agent available.

Warfarin

MECHANISM	Interferes with γ-carboxylation of vitamin K–dependent clotting factors II, VII, IX, and X, and proteins C and S. Metabolism affected by polymorphisms in the gene for vitamin K epoxide reductase complex (*VKORC1*). In laboratory assay, has effect on **EX**trinsic pathway and ↑ **PT**. Long half-life.	The **EX-P**residen**T** went to **war**(farin).
CLINICAL USE	Chronic anticoagulation (eg, venous thromboembolism prophylaxis, and prevention of stroke in atrial fibrillation). Not used in pregnant women (because warfarin, unlike heparin, crosses placenta). Follow PT/INR.	
ADVERSE EFFECTS  A	Bleeding, teratogenic, skin/tissue necrosis A, drug-drug interactions. Proteins C and S have shorter half-lives than clotting factors II, VII, IX, and X, resulting in early transient hypercoagulability with warfarin use. Skin/tissue necrosis within first few days of large doses believed to be due to small vessel microthrombosis.	For reversal of warfarin, give vitamin K. For rapid reversal, give fresh frozen plasma (FFP) or PCC. Heparin "bridging": heparin frequently used when starting warfarin. Heparin's activation of antithrombin enables anticoagulation during initial, transient hypercoagulable state caused by warfarin. Initial heparin therapy reduces risk of recurrent venous thromboembolism and skin/tissue necrosis.

Heparin vs warfarin

	Heparin	Warfarin
ROUTE OF ADMINISTRATION	Parenteral (IV, SC)	Oral
SITE OF ACTION	Blood	Liver
ONSET OF ACTION	Rapid (seconds)	Slow, limited by half-lives of normal clotting factors
MECHANISM OF ACTION	Activates antithrombin, which ↓ the action of IIa (thrombin) and factor Xa	Impairs synthesis of vitamin K–dependent clotting factors II, VII, IX, and X, and anti-clotting proteins C and S
DURATION OF ACTION	Hours	Days
AGENTS FOR REVERSAL	Protamine sulfate	Vitamin K, FFP, PCC
MONITORING	PTT (intrinsic pathway)	PT/INR (extrinsic pathway)
CROSSES PLACENTA	No	Yes (teratogenic)

Direct factor Xa inhibitors	ApiXaban, rivaroXaban.
MECHANISM	Bind to and directly inhibit factor Xa.
CLINICAL USE	Treatment and prophylaxis for DVT and PE; stroke prophylaxis in patients with atrial fibrillation. Oral agents do not usually require coagulation monitoring.
ADVERSE EFFECTS	Bleeding. Not easily reversible.

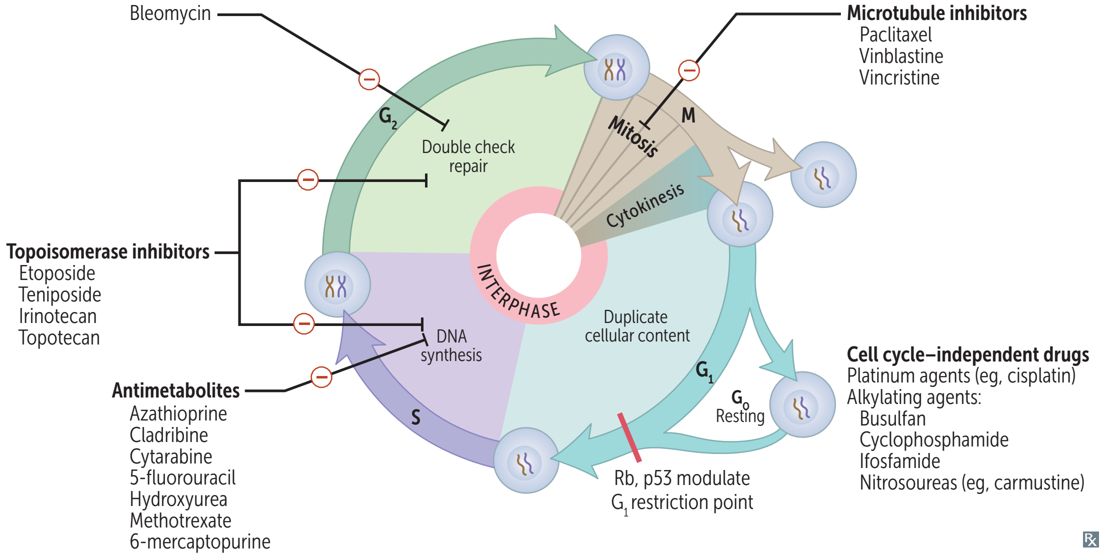
Thrombolytics	Alteplase (tPA), reteplase (rPA), streptokinase, tenecteplase (TNK-tPA).
MECHANISM	Directly or indirectly aid conversion of plasminogen to plasmin, which cleaves thrombin and fibrin clots. ↑ PT, ↑ PTT, no change in platelet count.
CLINICAL USE	Early MI, early ischemic stroke, direct thrombolysis of severe PE.
ADVERSE EFFECTS	Bleeding. Contraindicated in patients with active bleeding, history of intracranial bleeding, recent surgery, known bleeding diatheses, or severe hypertension. Nonspecific reversal with antifibrinolytics (eg, aminocaproic acid, tranexamic acid), platelet transfusions, and factor corrections (eg, cryoprecipitate, FFP, PCC).

ADP receptor inhibitors	Clopidogrel, prasugrel, ticagrelor (reversible), ticlopidine.
MECHANISM	Inhibit platelet aggregation by irreversibly blocking ADP ($P2Y_{12}$) receptor. Prevent expression of glycoproteins IIb/IIIa on platelet surface.
CLINICAL USE	Acute coronary syndrome; coronary stenting. ↓ incidence or recurrence of thrombotic stroke.
ADVERSE EFFECTS	Neutropenia (ticlopidine). TTP may be seen.

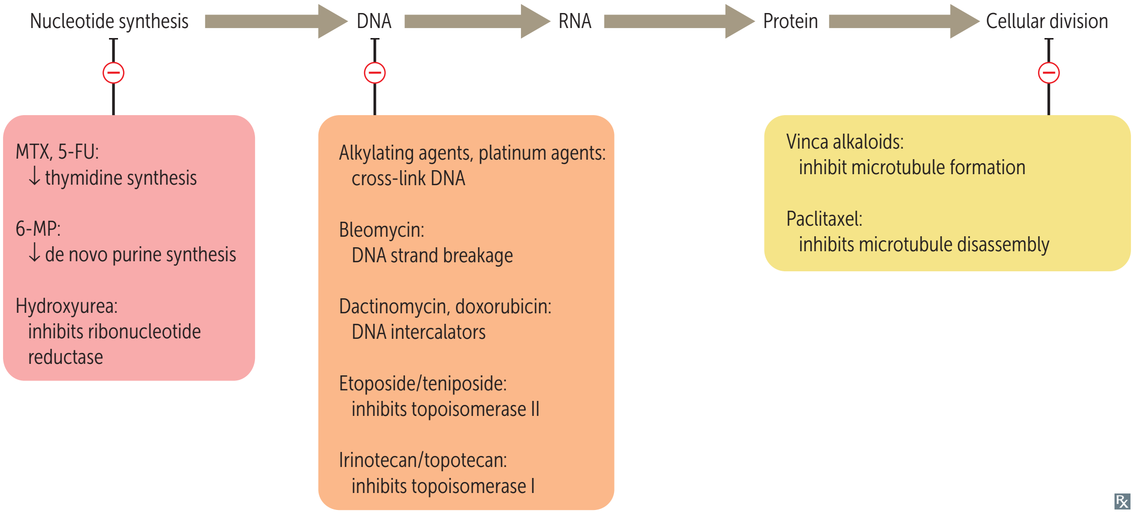
Cilostazol, dipyridamole	
MECHANISM	Phosphodiesterase inhibitors; ↑ cAMP in platelets, resulting in inhibition of platelet aggregation; vasodilators.
CLINICAL USE	Intermittent claudication, coronary vasodilation, prevention of stroke or TIAs (combined with aspirin).
ADVERSE EFFECTS	Nausea, headache, facial flushing, hypotension, abdominal pain.

Glycoprotein IIb/IIIa inhibitors	Abciximab, eptifibatide, tirofiban.
MECHANISM	Bind to the glycoprotein receptor IIb/IIIa on activated platelets, preventing aggregation. Abciximab is made from monoclonal antibody Fab fragments.
CLINICAL USE	Unstable angina, percutaneous coronary intervention.
ADVERSE EFFECTS	Bleeding, thrombocytopenia.

Cancer drugs—cell cycle


Bleomycin
Microtubule inhibitors
Paclitaxel
Vinblastine
Vincristine
M
Mitosis
G_2
Double check repair
Cytokinesis
Topoisomerase inhibitors
Etoposide
Teniposide
Irinotecan
Topotecan
INTERPHASE
DNA synthesis
Duplicate cellular content
Antimetabolites
Azathioprine
Cladribine
Cytarabine
5-fluorouracil
Hydroxyurea
Methotrexate
6-mercaptopurine
S
G_1
G_0
Resting
Cell cycle–independent drugs
Platinum agents (eg, cisplatin)
Alkylating agents:
Busulfan
Cyclophosphamide
Ifosfamide
Nitrosoureas (eg, carmustine)
Rb, p53 modulate
G_1 restriction point

Cancer drugs—targets


Nucleotide synthesis
DNA
RNA
Protein
Cellular division

MTX, 5-FU:
↓ thymidine synthesis

6-MP:
↓ de novo purine synthesis

Hydroxyurea:
inhibits ribonucleotide reductase

Alkylating agents, platinum agents:
cross-link DNA

Bleomycin:
DNA strand breakage

Dactinomycin, doxorubicin:
DNA intercalators

Etoposide/teniposide:
inhibits topoisomerase II

Irinotecan/topotecan:
inhibits topoisomerase I

Vinca alkaloids:
inhibit microtubule formation

Paclitaxel:
inhibits microtubule disassembly

Antimetabolites

DRUG	MECHANISM[a]	CLINICAL USE	ADVERSE EFFECTS
Azathioprine, 6-mercaptopurine	Purine (thiol) analogs → ↓ de novo purine synthesis. Activated by HGPRT. Azathioprine is metabolized into 6-MP.	Preventing organ rejection, rheumatoid arthritis, IBD, SLE; used to wean patients off steroids in chronic disease and to treat steroid-refractory chronic disease.	Myelosuppression, GI, liver. Azathioprine and 6-MP are metabolized by xanthine oxidase; thus both have ↑ toxicity with allopurinol or febuxostat.
Cladribine	Purine analog → multiple mechanisms (eg, inhibition of DNA polymerase, DNA strand breaks).	Hairy cell leukemia.	Myelosuppression, nephrotoxicity, and neurotoxicity.
Cytarabine (arabinofuranosyl cytidine)	Pyrimidine analog → inhibition of DNA polymerase.	Leukemias (AML), lymphomas.	Myelosuppression with megaloblastic anemia. CYTarabine causes panCYTopenia.
5-fluorouracil	Pyrimidine analog bioactivated to 5-FdUMP, which covalently complexes with thymidylate synthase and folic acid. Capecitabine is a prodrug with similar activity. This complex inhibits thymidylate synthase → ↓ dTMP → ↓ DNA synthesis.	Colon cancer, pancreatic cancer, basal cell carcinoma (topical). Effects enhanced with the addition of leucovorin.	Myelosuppression, palmar-plantar erythrodysesthesia (hand-foot syndrome).
Methotrexate	Folic acid analog that competitively inhibits dihydrofolate reductase → ↓ dTMP → ↓ DNA synthesis.	Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas. Non-neoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis.	Myelosuppression, which is reversible with leucovorin "rescue." Hepatotoxicity. Mucositis (eg, mouth ulcers). Pulmonary fibrosis.

[a] All are S-phase specific.

Antitumor antibiotics

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Bleomycin	Induces free radical formation → breaks in DNA strands.	Testicular cancer, Hodgkin lymphoma.	Pulmonary fibrosis, skin hyperpigmentation. Minimal myelosuppression.
Dactinomycin (actinomycin D)	Intercalates in DNA.	Wilms tumor, Ewing sarcoma, rhabdomyosarcoma. Used for childhood tumors.	Myelosuppression.
Doxorubicin, daunorubicin	Generate free radicals. Intercalate in DNA → breaks in DNA → ↓ replication.	Solid tumors, leukemias, lymphomas.	Cardiotoxicity (dilated cardiomyopathy), myelosuppression, alopecia. Dexrazoxane (iron chelating agent), used to prevent cardiotoxicity.

Alkylating agents

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Busulfan	Cross-links DNA.	CML. Also used to ablate patient's bone marrow before bone marrow transplantation.	Severe myelosuppression (in almost all cases), pulmonary fibrosis, hyperpigmentation.
Cyclophosphamide, ifosfamide	Cross-link DNA at guanine N-7. Require bioactivation by liver. A nitrogen mustard.	Solid tumors, leukemia, lymphomas.	Myelosuppression; hemorrhagic cystitis, prevented with mesna (thiol group of mesna binds toxic metabolites) or N-acetylcysteine.
Nitrosoureas	Require bioactivation. Cross blood-brain barrier → CNS. Cross-link DNA.	Brain tumors (including glioblastoma multiforme).	CNS toxicity (convulsions, dizziness, ataxia).

Microtubule inhibitors

DRUG	MECHANISM	CLINICAL USE	ADVERSE EFFECTS
Paclitaxel, other taxols	Hyperstabilize polymerized microtubules in M phase so that mitotic spindle cannot break down (anaphase cannot occur).	Ovarian and breast carcinomas.	Myelosuppression, neuropathy, hypersensitivity.
Vincristine, vinblastine	Vinca alkaloids that bind β-tubulin and inhibit its polymerization into microtubules → prevent mitotic spindle formation (M-phase arrest).	Solid tumors, leukemias, Hodgkin (vinblastine) and non-Hodgkin (vincristine) lymphomas.	Vincristine: neurotoxicity (areflexia, peripheral neuritis), constipation (including paralytic ileus).

Cisplatin, carboplatin

MECHANISM	Cross-link DNA.
CLINICAL USE	Testicular, bladder, ovary, and lung carcinomas.
ADVERSE EFFECTS	Nephrotoxicity, peripheral neuropathy, ototoxicity. Prevent nephrotoxicity with amifostine (free radical scavenger) and chloride (saline) diuresis.

Etoposide, teniposide

MECHANISM	Etoposide inhibits topoisomerase II → ↑ DNA degradation.
CLINICAL USE	Solid tumors (particularly testicular and small cell lung cancer), leukemias, lymphomas.
ADVERSE EFFECTS	Myelosuppression, alopecia.

Irinotecan, topotecan

MECHANISM	Inhibit topoisomerase I and prevent DNA unwinding and replication.
CLINICAL USE	Colon cancer (irinotecan); ovarian and small cell lung cancers (topotecan).
ADVERSE EFFECTS	Severe myelosuppression, diarrhea.

Hydroxyurea

MECHANISM	Inhibits ribonucleotide reductase → ↓ DNA Synthesis (S-phase specific).
CLINICAL USE	Myeloproliferative disorders (eg, CML, polycythemia vera), sickle cell (↑ HbF), melanoma.
ADVERSE EFFECTS	Severe myelosuppression.

Bevacizumab

MECHANISM	Monoclonal antibody against VEGF. Inhibits angiogenesis (**B**e**V**acizumab inhibits **B**lood **V**essel formation).
CLINICAL USE	Solid tumors (colorectal cancer, renal cell carcinoma).
ADVERSE EFFECTS	Hemorrhage, blood clots, and impaired wound healing.

Erlotinib

MECHANISM	EGFR tyrosine kinase inhibitor.
CLINICAL USE	Non-small cell lung carcinoma.
ADVERSE EFFECTS	Rash.

Cetuximab

MECHANISM	Monoclonal antibody against EGFR.
CLINICAL USE	Stage IV colorectal cancer (wild-type *KRAS*), head and neck cancer.
ADVERSE EFFECTS	Rash, elevated LFTs, diarrhea.

Imatinib

MECHANISM	Tyrosine kinase inhibitor of *BCR-ABL* (Philadelphia chromosome fusion gene in CML) and c-*kit* (common in GI stromal tumors).
CLINICAL USE	CML, GI stromal tumors (GIST).
ADVERSE EFFECTS	Fluid retention.

Rituximab

MECHANISM	Monoclonal antibody against CD20, which is found on most B-cell neoplasms.
CLINICAL USE	Non-Hodgkin lymphoma, CLL, ITP, rheumatoid arthritis.
ADVERSE EFFECTS	↑ risk of progressive multifocal leukoencephalopathy.

Bortezomib, carfilzomib

MECHANISM	Proteasome inhibitors, induce arrest at G2-M phase and apoptosis.
CLINICAL USE	Multiple myeloma, mantle cell lymphoma.
ADVERSE EFFECTS	Peripheral neuropathy, herpes zoster reactivation.

Tamoxifen, raloxifene

MECHANISM	Selective estrogen receptor modulators (SERMs)—receptor antagonists in breast and agonists in bone. Block the binding of estrogen to ER ⊕ cells.
CLINICAL USE	Breast cancer treatment (tamoxifen only) and prevention. Raloxifene also useful to prevent osteoporosis.
ADVERSE EFFECTS	Tamoxifen—partial agonist in endometrium, which ↑ the risk of endometrial cancer; "hot flashes." **Ralox**ifene—no ↑ in endometrial carcinoma (so you can **relax**!), because it is an estrogen receptor antagonist in endometrial tissue. Both ↑ risk of thromboembolic events (eg, DVT, PE).

Trastuzumab (Herceptin)

MECHANISM	Monoclonal antibody against HER-2 (*c-erbB2*), a tyrosine kinase receptor. Helps kill cancer cells that overexpress HER-2, through inhibition of HER2-initiated cellular signaling and antibody-dependent cytotoxicity.
CLINICAL USE	HER-**2** ⊕ breast cancer and gastric cancer (tras**2**zumab).
ADVERSE EFFECTS	Cardiotoxicity. "**Heart**ceptin" damages the **heart**.

Vemurafenib

MECHANISM	Small molecule inhibitor of *BRAF* oncogene ⊕ melanoma. **VEmuRAF-enib** is for **V**600**E**-**mu**tated ***BRAF* inhib**ition.
CLINICAL USE	Metastatic melanoma.

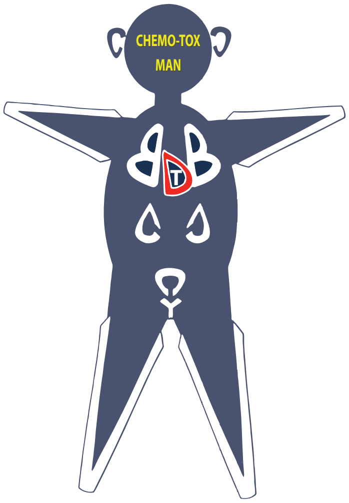
Tumor lysis syndrome

Oncologic emergency triggered by massive tumor cell lysis, most often in lymphomas/leukemias. Release of K^+ → hyperkalemia, release of PO_4^{3-} → hyperphosphatemia, hypocalcemia due to Ca^{2+} sequestration by PO_4^{3-}. ↑ nucleic acid breakdown → hyperuricemia → acute kidney injury. Treatments include aggressive hydration, allopurinol, rasburicase.

Rasburicase

MECHANISM	Recombinant uricase that catalyzes metabolism of uric acid to allantoin.
CLINICAL USE	Prevention and treatment of tumor lysis syndrome.

Common chemotoxicities



Cisplatin/**C**arboplatin → ototoxicity (and nephrotoxicity)

Vincristine → peripheral neuropathy
Bleomycin, **B**usulfan → pulmonary fibrosis
Doxorubicin → cardiotoxicity
Trastuzumab (Herceptin) → cardiotoxicity
Cisplatin/**C**arboplatin → nephrotoxicity (and ototoxicity)

CYclophosphamide → hemorrhagic cystitis

Musculoskeletal, Skin, and Connective Tissue

"Rigid, the skeleton of habit alone upholds the human frame."

—Virginia Woolf

"Beauty may be skin deep, but ugly goes clear to the bone."

—Redd Foxx

"The function of muscle is to pull and not to push, except in the case of the genitals and the tongue."

—Leonardo da Vinci

"To thrive in life you need three bones. A wishbone. A backbone. And a funny bone."

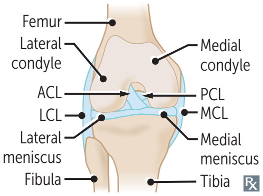
—Reba McEntire

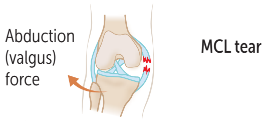
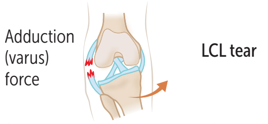
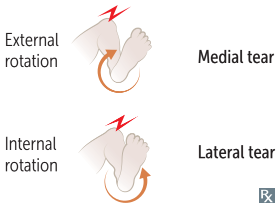
- Anatomy and Physiology 424
- Pathology 435
- Dermatology 446
- Pharmacology 455

▸ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—ANATOMY AND PHYSIOLOGY

Knee exam

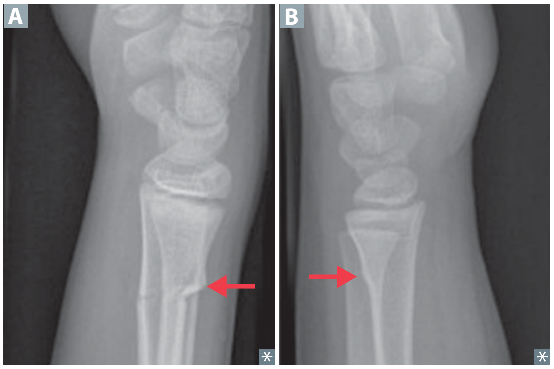
ACL: extends from lateral femoral condyle to anterior tibia.
PCL: extends from medial femoral condyle to posterior tibia.
Perform knee exam with patient supine.


Femur
Lateral condyle
ACL
LCL
Lateral meniscus
Fibula
Medial condyle
PCL
MCL
Medial meniscus
Tibia
Rx

TEST	PROCEDURE	
Anterior drawer sign	Bending knee at 90° angle, ↑ anterior gliding of tibia due to ACL injury. Lachman test is similar, but at 30° angle.	ACL tear Anterior drawer sign
Posterior drawer sign	Bending knee at 90° angle, ↑ posterior gliding of tibia due to PCL injury.	PCL tear Posterior drawer sign
Abnormal passive abduction	Knee either extended or at ~ 30° angle, lateral (valgus) force → medial space widening of tibia → MCL injury.	 Abduction (valgus) force MCL tear
Abnormal passive adduction	Knee either extended or at ~ 30° angle, medial (varus) force → lateral space widening of tibia → LCL injury.	 Adduction (varus) force LCL tear
McMurray test	During flexion and extension of knee with rotation of tibia/foot: ▪ Pain, "popping" on external rotation → medial meniscal tear ▪ Pain, "popping" on internal rotation → lateral meniscal tear	 External rotation Medial tear Internal rotation Lateral tear Rx

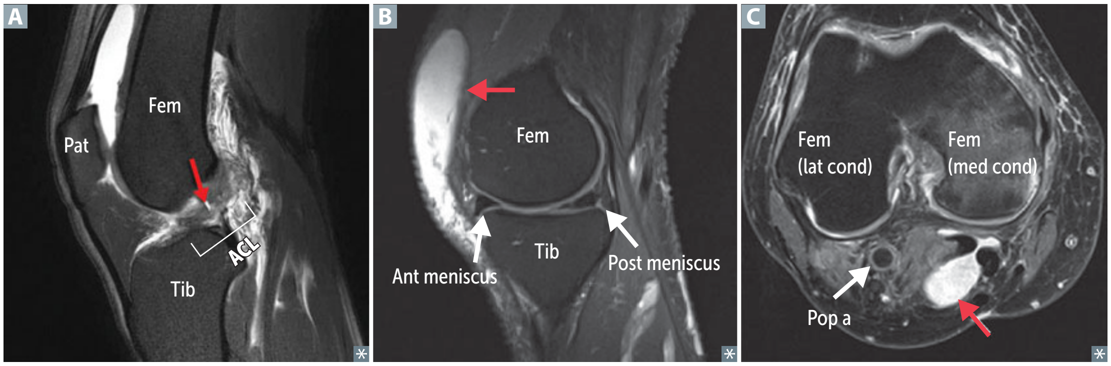
Common pediatric fractures

Greenstick fracture	Incomplete fracture extending partway through width of bone **A** following bending stress; bone is bent like a **green twig**.
Torus fracture	Axial force applied to immature bone → simple buckle fracture of cortex **B**. Can be very subtle.

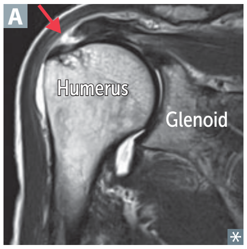


Common knee conditions

"Unhappy triad"	Common injury in contact sports due to lateral force applied to a planted leg. Classically, consists of damage to the ACL A, MCL, and medial meniscus (attached to MCL); however, lateral meniscus injury is more common. Presents with acute knee pain and signs of joint injury/instability.
Prepatellar bursitis	Inflammation of the prepatellar bursa in front of the kneecap B. Can be caused by repeated trauma or pressure from excessive kneeling (also called "housemaid's knee").
Baker cyst	Popliteal fluid collection (arrow in C) in gastrocnemius-semimembranosus bursa commonly communicating with synovial space and related to chronic joint disease.


A
Fem
Pat
ACL
Tib
B
Fem
Tib
Ant meniscus
Post meniscus
C
Fem (lat cond)
Fem (med cond)
Pop a

Rotator cuff muscles

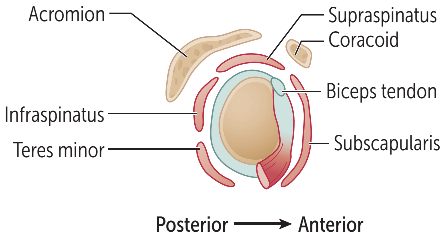

A
Humerus
Glenoid

Shoulder muscles that form the rotator cuff:

- Supraspinatus (suprascapular nerve)—abducts arm initially (before the action of the deltoid); most common rotator cuff injury (trauma or degeneration and impingement → tendinopathy or tear [arrow in A]), assessed by "empty/full can" test.
- Infraspinatus (suprascapular nerve)—laterally rotates arm; pitching injury.
- teres minor (axillary nerve)—adducts and laterally rotates arm.
- Subscapularis (upper and lower subscapular nerves)—medially rotates and adducts arm.

Innervated primarily by C5-C6.

SItS (small t is for teres minor).

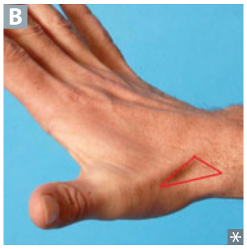
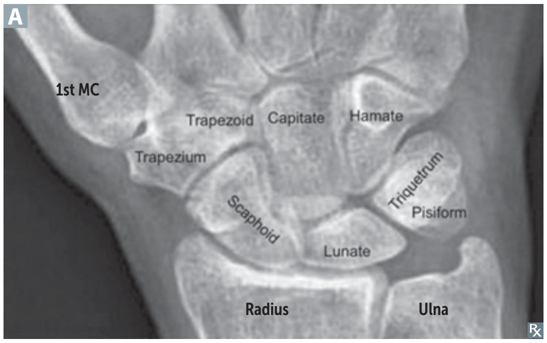

Acromion
Supraspinatus
Coracoid
Biceps tendon
Infraspinatus
Teres minor
Subscapularis
Posterior
Anterior

Arm abduction

DEGREE	MUSCLE	NERVE
0°–15°	Supraspinatus	Suprascapular
15°–100°	Deltoid	Axillary
> 90°	Trapezius	Accessory
> 100°	Serratus anterior	Long thoracic

Overuse injuries of the elbow

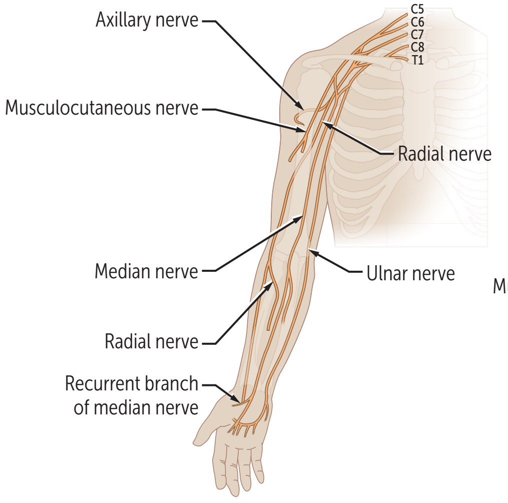
Medial epicondylitis (golfer's elbow)	Repetitive flexion (forehand shots) or idiopathic → pain near medial epicondyle.
Lateral epicondylitis (tennis elbow)	Repetitive extension (backhand shots) or idiopathic → pain near lateral epicondyle.

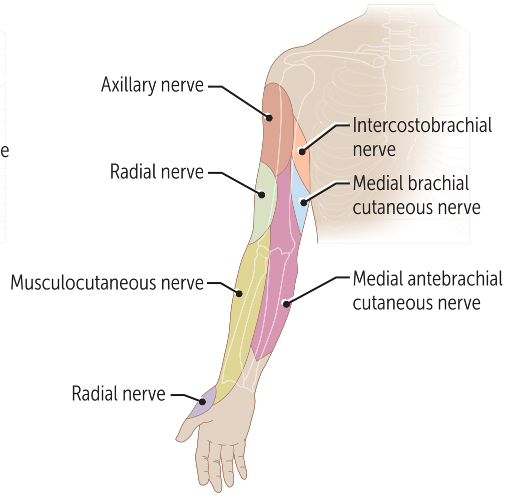
Wrist bones  	**S**caphoid, **L**unate, **T**riquetrum, **P**isiform, **H**amate, **C**apitate, **T**rapezoid, **T**rapezium A. (**S**o **L**ong **T**o **P**inky, **H**ere **C**omes **T**he **T**humb). Scaphoid (palpable in anatomic snuff box B) is the most commonly fractured carpal bone, typically due to a fall on an outstretched hand. Complications of proximal scaphoid fractures include avascular necrosis and nonunion due to retrograde blood supply. Dislocation of lunate may cause acute carpal tunnel syndrome.  A 1st MC Trapezoid Capitate Hamate Trapezium Triquetrum Pisiform Scaphoid Lunate Radius Ulna
Carpal tunnel syndrome	Entrapment of median nerve in carpal tunnel; nerve compression → paresthesia, pain, and numbness in distribution of median nerve (thenar eminence atrophies but sensation spared, because palmar cutaneous branch enters the hand external to carpal tunnel). Associated with pregnancy (due to edema), rheumatoid arthritis, hypothyroidism, diabetes, acromegaly, dialysis-related amyloidosis; may be associated with repetitive use. Suggested by ⊕ Tinel sign (percussion of wrist causes tingling) and Phalen maneuver (90° flexion of wrist causes tingling).
Guyon canal syndrome	Compression of ulnar nerve at wrist or hand. Classically seen in cyclists due to pressure from handlebars.

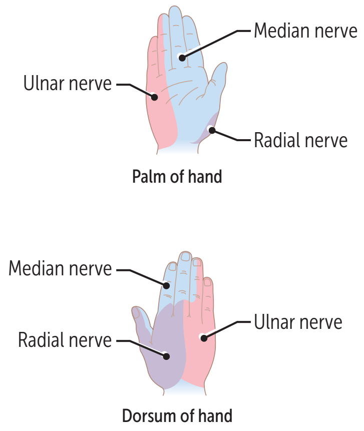
Upper extremity nerves

NERVE	CAUSES OF INJURY	PRESENTATION
Axillary (C5-C6)	Fractured surgical neck of humerus; anterior dislocation of humerus	Flattened deltoid Loss of arm abduction at shoulder (> 15°) Loss of sensation over deltoid muscle and lateral arm
Musculocutaneous (C5-C7)	Upper trunk compression	Loss of forearm flexion and supination Loss of sensation over lateral forearm
Radial (C5-T1)	Midshaft fracture of humerus; compression of axilla, eg, due to crutches or sleeping with arm over chair ("Saturday night palsy")	Wrist drop: loss of elbow, wrist, and finger extension ↓ grip strength (wrist extension necessary for maximal action of flexors) Loss of sensation over posterior arm/forearm and dorsal hand
Median (C5-T1)	Supracondylar fracture of humerus (proximal lesion); carpal tunnel syndrome and wrist laceration (distal lesion)	"Ape hand" and "Pope's blessing" Loss of wrist flexion, flexion of lateral fingers, thumb opposition, lumbricals of 2nd and 3rd digits Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral 3½ fingers with proximal lesion
Ulnar (C8-T1)	Fracture of medial epicondyle of humerus "funny bone" (proximal lesion); fractured hook of hamate (distal lesion) from fall on outstretched hand	"Ulnar claw" on digit extension Radial deviation of wrist upon flexion (proximal lesion) Loss of wrist flexion, flexion of medial fingers, abduction and adduction of fingers (interossei), actions of medial 2 lumbrical muscles Loss of sensation over medial 1½ fingers including hypothenar eminence
Recurrent branch of median nerve (C5-T1)	Superficial laceration of palm	"Ape hand" Loss of thenar muscle group: opposition, abduction, and flexion of thumb No loss of sensation

Humerus fractures, proximally to distally, follow the **ARM** (**A**xillary → **R**adial → **M**edian)

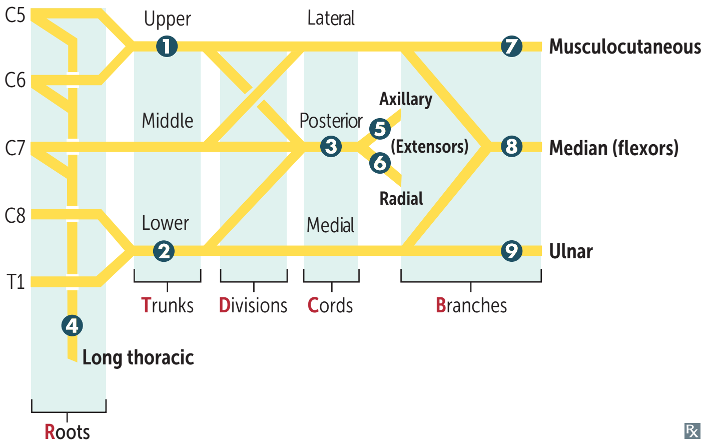

Axillary nerve
C5
C6
C7
C8
T1
Musculocutaneous nerve
Radial nerve
Median nerve
Ulnar nerve
Radial nerve
Recurrent branch of median nerve


Axillary nerve
Intercostobrachial nerve
Radial nerve
Medial brachial cutaneous nerve
Musculocutaneous nerve
Medial antebrachial cutaneous nerve
Radial nerve

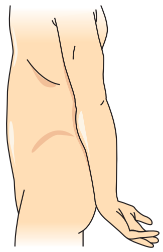
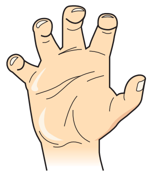
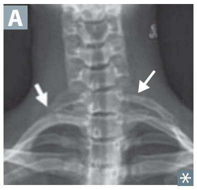
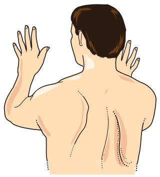

Median nerve
Ulnar nerve
Radial nerve
Palm of hand
Median nerve
Ulnar nerve
Radial nerve
Dorsum of hand

Brachial plexus lesions

❶ Erb palsy ("waiter's tip")
❷ Klumpke palsy (claw hand)
❸ Wrist drop
❹ Winged scapula
❺ Deltoid paralysis
❻ "Saturday night palsy" (wrist drop)
❼ Difficulty flexing elbow, variable sensory loss
❽ Decreased thumb function, "Pope's blessing"
❾ Intrinsic muscles of hand, claw hand


C5
C6
C7
C8
T1
Upper
Middle
Lower
Lateral
Posterior
Medial
1
2
3
4
5
6
7
8
9
Axillary
(Extensors)
Radial
Musculocutaneous
Median (flexors)
Ulnar
Long thoracic
Trunks
Divisions
Cords
Branches
Roots

Randy
Travis
Drinks
Cold
Beer

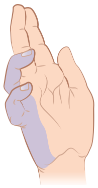
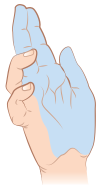
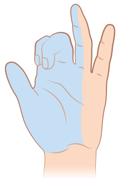
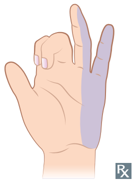
CONDITION	INJURY	CAUSES	MUSCLE DEFICIT	FUNCTIONAL DEFICIT	PRESENTATION
Erb palsy ("waiter's tip")	Traction or tear of **upper** ("**Erb**-er") trunk: C5-C6 roots	Infants—lateral traction on neck during delivery Adults—trauma	Deltoid, supraspinatus Infraspinatus Biceps brachii	Abduction (arm hangs by side) Lateral rotation (arm medially rotated) Flexion, supination (arm extended and pronated)	
Klumpke palsy	Traction or tear of **lower** trunk: C8-T1 root	Infants—upward force on arm during delivery Adults—trauma (eg, grabbing a tree branch to break a fall)	Intrinsic hand muscles: lumbricals, interossei, thenar, hypothenar	Total claw hand: lumbricals normally flex MCP joints and extend DIP and PIP joints	
Thoracic outlet syndrome	Compression of **lower** trunk and subclavian vessels	Cervical rib (arrows in A), Pancoast tumor	Same as Klumpke palsy	Atrophy of intrinsic hand muscles; ischemia, pain, and edema due to vascular compression	 A
Winged scapula	Lesion of long thoracic nerve	Axillary node dissection after mastectomy, stab wounds	Serratus anterior	Inability to anchor scapula to thoracic cage → cannot abduct arm above horizontal position	

Distortions of the hand

At rest, a balance exists between the extrinsic flexors and extensors of the hand, as well as the intrinsic muscles of the hand—particularly the lumbrical muscles (flexion of MCP, extension of DIP and PIP joints).

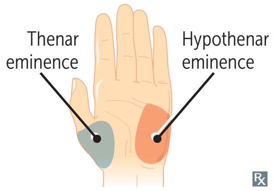
“Clawing”—seen best with **distal** lesions of median or ulnar nerves. Remaining extrinsic flexors of the digits exaggerate the loss of the lumbricals → fingers extend at MCP, flex at DIP and PIP joints.

Deficits less pronounced in **proximal** lesions; deficits present during voluntary flexion of the digits.

PRESENTATION				
CONTEXT	Extending fingers/at rest	Making a fist	Extending fingers/at rest	Making a fist
LOCATION OF LESION	Distal ulnar nerve	Proximal median nerve	Distal median nerve	Proximal ulnar nerve
SIGN	“Ulnar claw”	“Pope’s blessing”	“Median claw”	“OK gesture”

Note: Atrophy of the thenar eminence (unopposable thumb → “ape hand”) can be seen in median nerve lesions, while atrophy of the hypothenar eminence can be seen in ulnar nerve lesions.

Hand muscles



Thenar (median)—**O**pponens pollicis, **A**bductor pollicis brevis, **F**lexor pollicis brevis, superficial head (deep head by ulnar nerve).

Hypothenar (ulnar)—**O**pponens digiti minimi, **A**bductor digiti minimi, **F**lexor digiti minimi brevis.

Both groups perform the same functions: **O**ppose, **A**bduct, and **F**lex (**OAF**).

Dorsal interossei—abduct the fingers.

DAB = **D**orsals **AB**duct.

Palmar interossei—adduct the fingers.

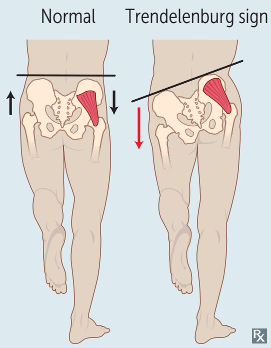
PAD = **P**almars **AD**duct.

Lumbricals—flex at the MCP joint, extend PIP and DIP joints.

Lower extremity nerves

NERVE	INNERVATION	CAUSE OF INJURY	PRESENTATION/COMMENTS
Iliohypogastric (T12-L1)	Sensory—suprapubic region Motor—transversus abdominis and internal oblique	Abdominal surgery	Burning or tingling pain in surgical incision site radiating to inguinal and suprapubic region
Genitofemoral nerve (L1-L2)	Sensory—scrotum/labia majora, medial thigh Motor—cremaster	Laparoscopic surgery	↓ anterior thigh sensation beneath inguinal ligament; absent cremasteric reflex
Lateral femoral cutaneous (L2-L3)	Sensory—anterior and lateral thigh	Tight clothing, obesity, pregnancy	↓ thigh sensation (anterior and lateral)
Obturator (L2-L4)	Sensory—medial thigh Motor—obturator externus, adductor longus, adductor brevis, gracilis, pectineus, adductor magnus	Pelvic surgery	↓ thigh sensation (medial) and adduction
Femoral (L2-L4)	Sensory—anterior thigh, medial leg Motor—quadriceps, iliopsoas, pectineus, sartorius	Pelvic fracture	↓ thigh flexion and leg extension
Sciatic (L4-S3)	Sensory—posterior thigh Motor—semitendinosus, semimembranosus, biceps femoris, adductor magnus	Herniated disc	Splits into common peroneal and tibial nerves
Common peroneal (L4-S2)	Sensory—dorsum of foot Motor—biceps femoris, tibialis anterior, extensor muscles of foot	Trauma or compression of lateral aspect of leg, fibular neck fracture	**PED** = **P**eroneal **E**verts and **D**orsiflexes; if injured, foot drop**PED** Loss of sensation on dorsum of foot **Foot drop**—inverted and plantarflexed at rest, loss of eversion and dorsiflexion; "steppage gait"
Tibial (L4-S3)	Sensory—sole of foot Motor—triceps surae, plantaris, popliteus, flexor muscles of foot	Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion)	**TIP** = **T**ibial **I**nverts and **P**lantarflexes; if injured, can't stand on **TIP**toes Inability to curl toes and loss of sensation on sole; in proximal lesions, foot everted at rest with loss of inversion and plantarflexion

Lower extremity nerves *(continued)*

NERVE	INNERVATION	CAUSE OF INJURY	PRESENTATION/COMMENTS
Superior gluteal (L4-S1)  	Motor—gluteus medius, gluteus minimus, tensor fascia latae	Iatrogenic injury during intramuscular injection to upper medial gluteal region	Trendelenburg sign/gait—pelvis tilts because weight-bearing leg cannot maintain alignment of pelvis through hip abduction Lesion is contralateral to the side of the hip that drops, ipsilateral to extremity on which the patient stands Choose superolateral quadrant (ideally the anterolateral region) as intramuscular injection site to avoid nerve injury
Inferior gluteal (L5-S2)	Motor—gluteus maximus	Posterior hip dislocation	Difficulty climbing stairs, rising from seated position; loss of hip extension
Pudendal (S2-S4)	Sensory—perineum Motor—external urethral and anal sphincters	Stretch injury during childbirth	↓ sensation in perineum and genital area; can cause fecal or urinary incontinence Can be blocked with local anesthetic during childbirth using ischial spine as a landmark for injection

Actions of hip muscles

ACTION	MUSCLES
Abductors	Gluteus medius, gluteus minimus
Adductors	Adductor magnus, adductor longus, adductor brevis
Extensors	Gluteus maximus, semitendinosus, semimembranosus
Flexors	Iliopsoas, rectus femoris, tensor fascia lata, pectineus
Internal rotation	Gluteus medius, gluteus minimus, tensor fascia latae
External rotation	Iliopsoas, gluteus maximus, piriformis, obturator

Signs of lumbosacral radiculopathy

Paresthesia and weakness related to specific lumbosacral spinal nerves. Usually, the intervertebral disc herniates into the central canal, affecting the inferior nerves (eg, herniation of L3/4 disc affects L4 spinal nerve, but not L3).

Intervertebral discs generally herniate posterolaterally, due to the thin posterior longitudinal ligament and thicker anterior longitudinal ligament along the midline of the vertebral bodies.

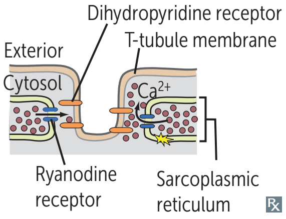
DISC LEVEL	FINDINGS
L3–L4	Weakness of knee extension, ↓ patellar reflex
L4–L5	Weakness of dorsiflexion, difficulty in heel-walking
L5–S1	Weakness of plantar flexion, difficulty in toe-walking, ↓ Achilles reflex

Neurovascular pairing

Nerves and arteries are frequently named together by the bones/regions with which they are associated. The following are exceptions to this naming convention.

LOCATION	NERVE	ARTERY
Axilla/lateral thorax	Long thoracic	Lateral thoracic
Surgical neck of humerus	Axillary	Posterior circumflex
Midshaft of humerus	Radial	Deep brachial
Distal humerus/ cubital fossa	Median	Brachial
Popliteal fossa	Tibial	Popliteal
Posterior to medial malleolus	Tibial	Posterior tibial

Muscle conduction to contraction

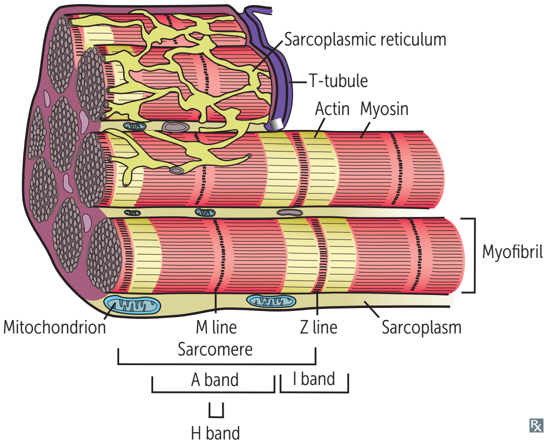

Dihydropyridine receptor
T-tubule membrane
Exterior
Cytosol
Ca^{2+}
Ryanodine receptor
Sarcoplasmic reticulum

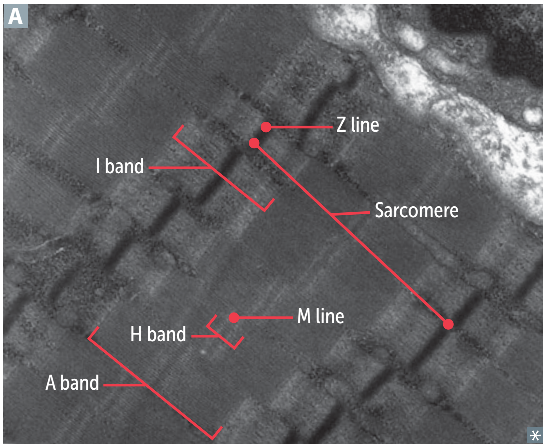
T-tubules are extensions of plasma membrane juxtaposed with terminal cisternae of the sarcoplasmic reticulum, allowing for coordinated contraction of muscles.

In skeletal muscle, 1 T-tubule + 2 terminal cisternae = triad.

In cardiac muscle, 1 T-tubule + 1 terminal cisterna = dyad.

1. Action potential depolarization opens presynaptic voltage-gated Ca^{2+} channels, inducing neurotransmitter release.
2. Postsynaptic ligand binding leads to muscle cell depolarization in the motor end plate.
3. Depolarization travels along muscle cell and down the T-tubule.
4. Depolarization of the voltage-sensitive dihydropyridine receptor, mechanically coupled to the ryanodine receptor on the sarcoplasmic reticulum, induces a conformational change in both receptors, causing Ca^{2+} release from sarcoplasmic reticulum.
5. Released Ca^{2+} binds to troponin C, causing a conformational change that moves tropomyosin out of the myosin-binding groove on actin filaments.
6. Myosin releases bound ADP and P_i → displacement of myosin on the actin filament (power stroke). Contraction results in shortening of **H** and **I** bands and between **Z** lines (**HIZ** shrinkage), but the A band remains the same length (**A** band is **A**lways the same length) **A**.
7. Binding of a new ATP molecule causes detachment of myosin head from actin filament. Hydrolysis of bound ATP → ADP, myosin head adopts high-energy position ("cocked") for the next contraction cycle.

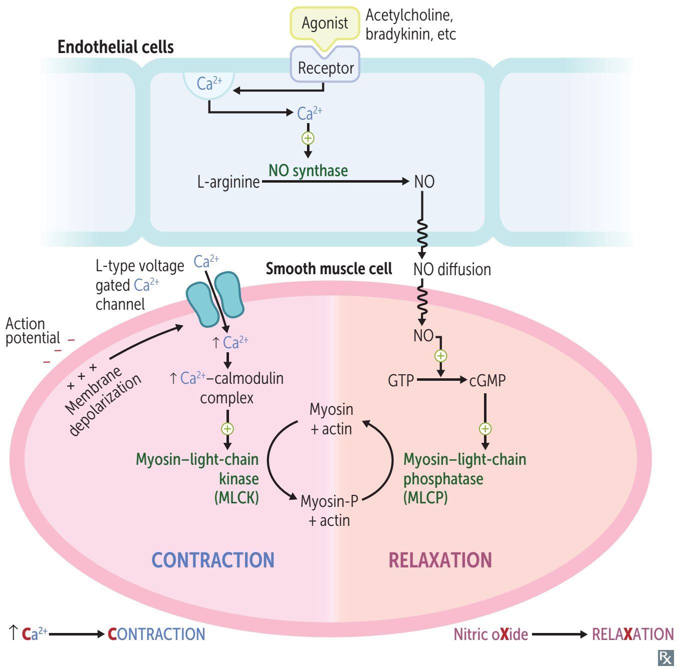

Sarcoplasmic reticulum
T-tubule
Actin
Myosin
Myofibril
Mitochondrion
M line
Z line
Sarcoplasm
Sarcomere
A band
I band
H band


A
Z line
I band
Sarcomere
M line
H band
A band

Types of muscle fibers

Type 1 muscle	**Slow** twitch; **red** fibers resulting from ↑ mitochondria and myoglobin concentration (↑ **ox**idative phosphorylation) → sustained contraction. Proportion ↑ after endurance training.	Think "**1 slow red ox**."
Type 2 muscle	Fast twitch; white fibers resulting from ↓ mitochondria and myoglobin concentration (↑ anaerobic glycolysis). Proportion ↑ after weight/resistance training, sprinting.	

Smooth muscle contraction


Agonist
Acetylcholine, bradykinin, etc
Endothelial cells
Receptor
Ca^{2+}
Ca^{2+}
L-arginine
NO synthase
NO
L-type voltage gated Ca^{2+} channel
Ca^{2+}
Smooth muscle cell
NO diffusion
Action potential
Membrane depolarization
↑ Ca^{2+}
↑ Ca^{2+}–calmodulin complex
NO
GTP
cGMP
Myosin + actin
Myosin–light-chain kinase (MLCK)
Myosin-P + actin
Myosin–light-chain phosphatase (MLCP)
CONTRACTION
RELAXATION
↑ Ca^{2+} → CONTRACTION
Nitric oXide → RELAXATION

Bone formation

Endochondral ossification	Bones of axial skeleton, appendicular skeleton, and base of skull. Cartilaginous model of bone is first made by chondrocytes. Osteoclasts and osteoblasts later replace with woven bone and then remodel to lamellar bone. In adults, woven bone occurs after fractures and in Paget disease. Defective in achondroplasia.
Membranous ossification	Bones of calvarium, facial bones, and clavicle. Woven bone formed directly without cartilage. Later remodeled to lamellar bone.

Cell biology of bone

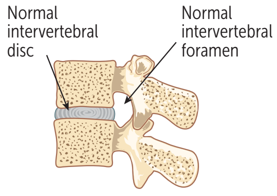
Osteoblast	Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP. Differentiates from mesenchymal stem cells in periosteum. Osteoblastic activity measured by bone ALP, osteocalcin, propeptides of type I procollagen.
Osteoclast	Dissolves bone by secreting H^+ and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors.
Parathyroid hormone	At low, intermittent levels, exerts anabolic effects (building bone) on osteoblasts and osteoclasts (indirect). Chronically ↑ PTH levels (1° hyperparathyroidism) cause catabolic effects (osteitis fibrosa cystica).
Estrogen	Inhibits apoptosis in bone-forming osteoblasts and induces apoptosis in bone-resorbing osteoclasts. Causes closure of epiphyseal plate during puberty. Estrogen deficiency (surgical or postmenopausal) → ↑ cycles of remodeling and bone resorption → ↑ risk of osteoporosis.

▸ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PATHOLOGY

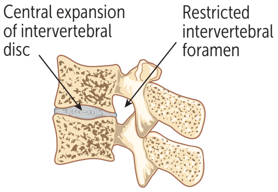
Achondroplasia

Failure of longitudinal bone growth (endochondral ossification) → short limbs. Membranous ossification is affected → large head relative to limbs. Constitutive activation of fibroblast growth factor receptor (FGFR3) actually inhibits chondrocyte proliferation. > 85% of mutations occur sporadically; autosomal dominant with full penetrance (homozygosity is lethal). Most common cause of dwarfism.

Osteoporosis



Normal vertebrae


Central expansion of intervertebral disc
Restricted intervertebral foramen

Mild compression fracture

Trabecular (spongy) and cortical bone lose mass and interconnections despite normal bone mineralization and lab values (serum Ca^{2+} and PO$_4^{3-}$).

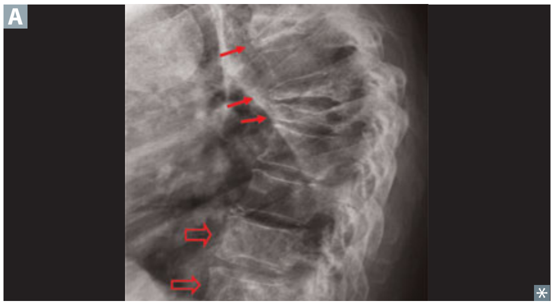
Most commonly due to ↑ bone resorption related to ↓ estrogen levels and old age. Can be secondary to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy) or other medical conditions (eg, hyperparathyroidism, hyperthyroidism, multiple myeloma, malabsorption syndromes).

Diagnosed by a bone mineral density scan (dual-energy x-ray absorptiometry [DEXA]) with a T-score of ≤ –2.5 or by a fragility fracture of hip or vertebra. Screening recommended in women > 65 years old.

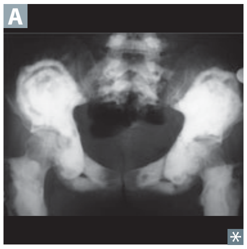
Prophylaxis: regular weight-bearing exercise and adequate Ca^{2+} and vitamin D intake throughout adulthood.

Treatment: bisphosphonates, teriparatide, SERMs, rarely calcitonin; denosumab (monoclonal antibody against RANKL).

Can lead to vertebral compression fractures (A, small arrows; large arrows show normal-for-age vertebral body height for comparison)—acute back pain, loss of height, kyphosis. Also can present with fractures of femoral neck, distal radius (Colles fracture).

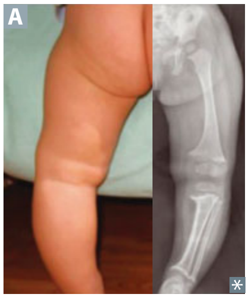


Osteopetrosis



Failure of normal bone resorption due to defective osteoclasts → thickened, dense bones that are prone to fracture. Defective osteoclasts cause overgrowth and sclerosis of cortical bone. Bone fills marrow space → pancytopenia, extramedullary hematopoiesis. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. X-rays show diffuse symmetric skeletal sclerosis (bone-in-bone, "stone bone" A). Can result in cranial nerve impingement and palsies as a result of narrowed foramina. Bone marrow transplant is potentially curative as osteoclasts are derived from monocytes.

Osteomalacia/rickets

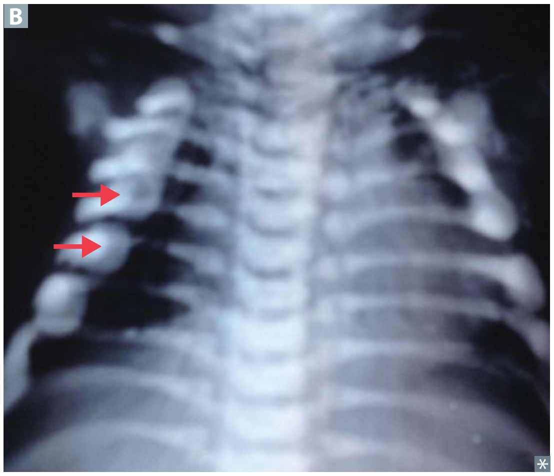


Defective mineralization of osteoid (osteomalacia) or cartilaginous growth plates (rickets, only in children). Most commonly due to vitamin D deficiency.

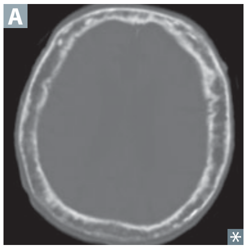
X-rays show osteopenia and "Looser zones" (pseudofractures) in osteomalacia, epiphyseal widening and metaphyseal cupping/fraying in rickets. Children with rickets have pathologic bow legs (genu varum A), bead-like costochondral junctions (rachitic rosary B), craniotabes (soft skull).

↓ vitamin D → ↓ serum Ca^{2+} → ↑ PTH secretion → ↓ serum PO_4^{3-}.

Hyperactivity of osteoblasts → ↑ ALP.



Paget disease of bone (osteitis deformans)



Common, localized disorder of bone remodeling caused by ↑ osteoclastic activity followed by ↑ osteoblastic activity that forms poor-quality bone. Serum Ca^{2+}, phosphorus, and PTH levels are normal. ↑ ALP. Mosaic pattern of woven and lamellar bone (osteocytes within lacunae in chaotic juxtapositions); long bone chalk-stick fractures. ↑ blood flow from ↑ arteriovenous shunts may cause high-output heart failure. ↑ risk of osteogenic sarcoma.

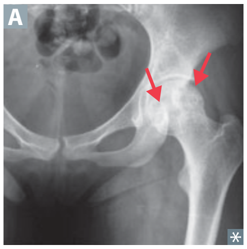
Hat size can be increased due to skull thickening A; hearing loss is common due to auditory foramen narrowing.

Stages of Paget disease:

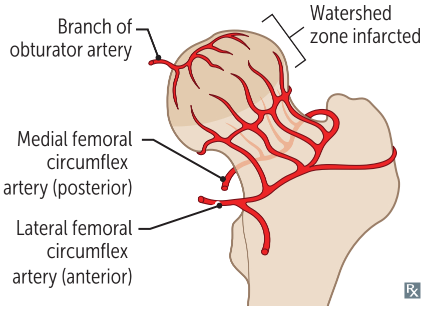
- Lytic—osteoclasts
- Mixed—osteoclasts + osteoblasts
- Sclerotic—osteoblasts
- Quiescent—minimal osteoclast/osteoblast activity

Treatment: bisphosphonates.

Osteonecrosis (avascular necrosis)



Infarction of bone and marrow, usually very painful. Most common site is femoral head A (due to insufficiency of medial circumflex femoral artery). Causes include **C**orticosteroids, **A**lcoholism, **S**ickle cell disease, **T**rauma, "the **B**ends" (caisson/decompression disease), **LE**gg-Calvé-Perthes disease (idiopathic), **G**aucher disease, **S**lipped capital femoral epiphysis—**CAST B**ent **LEGS**.

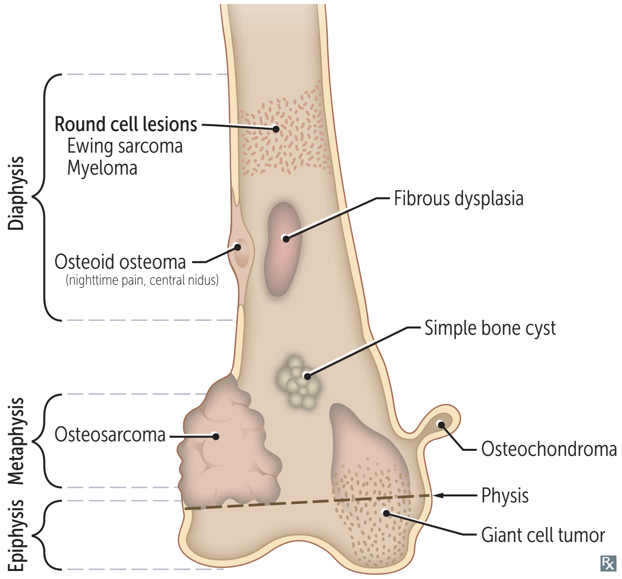

Branch of obturator artery
Watershed zone infarcted
Medial femoral circumflex artery (posterior)
Lateral femoral circumflex artery (anterior)

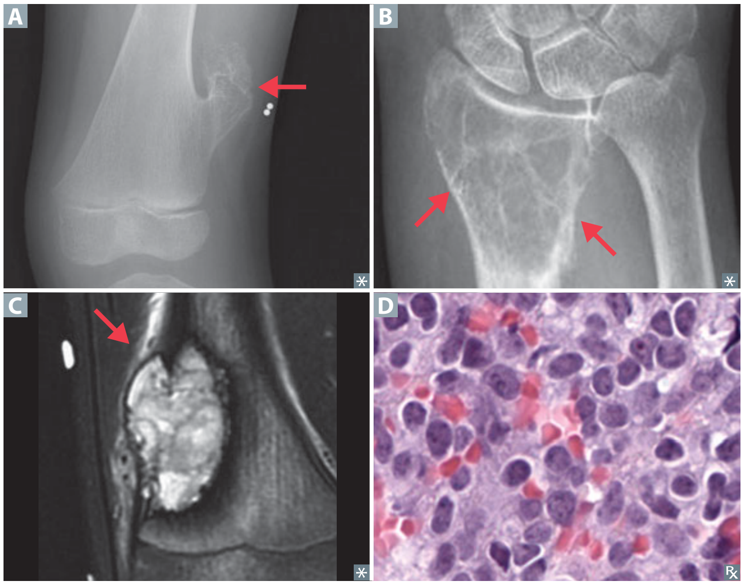
Lab values in bone disorders

DISORDER	SERUM Ca^{2+}	PO_4^{3-}	ALP	PTH	COMMENTS
Osteoporosis	—	—	—	—	↓ bone mass
Osteopetrosis	—/↓	—	—	—	Dense, brittle bones. Ca^{2+} ↓ in severe, malignant disease
Paget disease of bone	—	—	↑	—	Abnormal "mosaic" bone architecture
Osteitis fibrosa cystica					"Brown tumors" due to fibrous replacement of bone, subperiosteal thinning
Primary hyperparathyroidism	↑	↓	↑	↑	Idiopathic or parathyroid hyperplasia, adenoma, carcinoma
Secondary hyperparathyroidism	↓	↑	↑	↑	Often as compensation for CKD (↓ PO_4^{3-} excretion and production of activated vitamin D)
Osteomalacia/rickets	↓	↓	↑	↑	Soft bones; vitamin D deficiency also causes 2° hyperparathyroidism
Hypervitaminosis D	↑	↑	—	↓	Caused by oversupplementation or granulomatous disease (eg, sarcoidosis)

Primary bone tumors

TUMOR TYPE	EPIDEMIOLOGY/LOCATION	CHARACTERISTICS
Benign tumors		
Osteochondroma	Most common benign bone tumor. Males < 25 years old.	Bony exostosis with cartilaginous (chondroid) cap A. Rarely transforms to chondrosarcoma.
Giant cell tumor	20–40 years old. Epiphysis of long bones (often in knee region). Arises most commonly at distal femur and proximal tibia. "Osteoclastoma."	Locally aggressive benign tumor. "Soap bubble" appearance on x-ray B. Multinucleated giant cells that express RANKL.
Malignant tumors		
Osteosarcoma (osteogenic sarcoma)	One of the most common malignant bone tumors. Bimodal distribution: 10–20 years old (1°), > 65 (2°). Predisposing factors: Paget disease of bone, bone infarcts, radiation, familial retinoblastoma, Li-Fraumeni syndrome (germline *p53* mutation). Metaphysis of long bones, often around knee C.	Codman triangle (from elevation of periosteum) or sunburst pattern on x-ray. Aggressive. Treat with surgical en bloc resection (with limb salvage) and chemotherapy.
Ewing sarcoma	Boys < 15 years old. Commonly appears in diaphysis of long bones, pelvis, scapula, ribs.	Anaplastic small blue cell malignant tumor D. Extremely aggressive with early metastases, but responsive to chemotherapy. "Onion skin" periosteal reaction in bone. Associated with t(11;22) translocation causing fusion protein EWS-FLI 1. 11 + 22 = 33 (Patrick Ewing's jersey number).

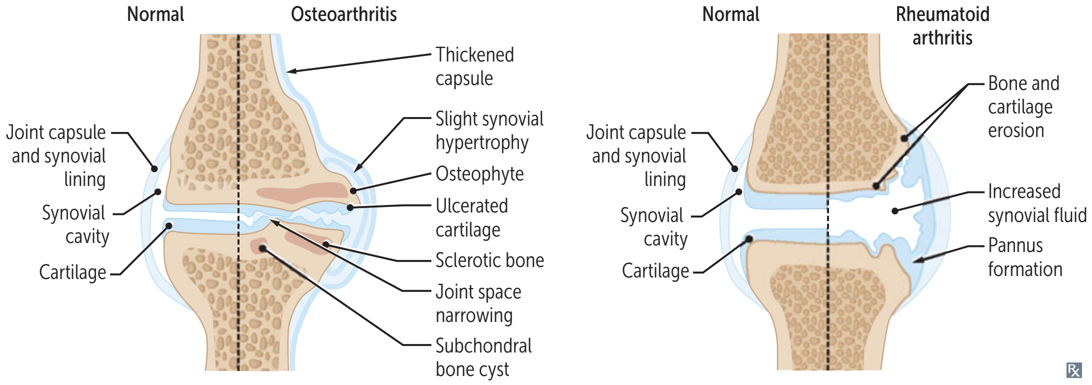

Diaphysis
Round cell lesions
Ewing sarcoma
Myeloma
Osteoid osteoma
(nighttime pain, central nidus)
Fibrous dysplasia
Simple bone cyst
Metaphysis
Osteosarcoma
Osteochondroma
Physis
Epiphysis
Giant cell tumor

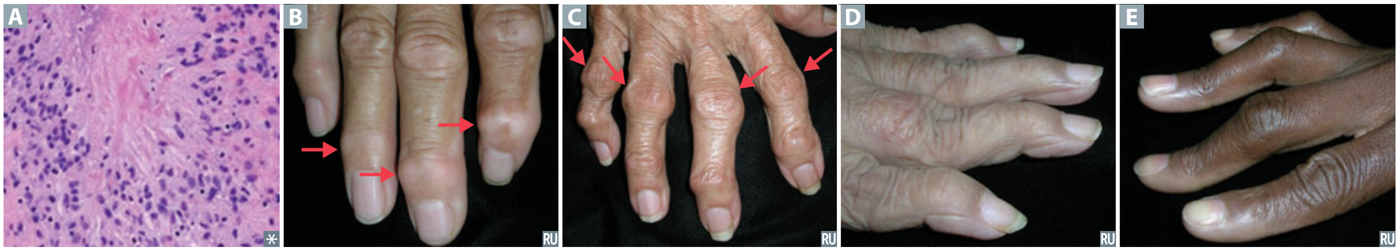


Osteoarthritis and rheumatoid arthritis

	Osteoarthritis	Rheumatoid arthritis
PATHOGENESIS	Mechanical—wear and tear destroys articular cartilage (degenerative joint disorder) → inflammation with inadequate repair. Chondrocytes mediate degradation and inadequate repair.	Autoimmune—inflammation induces formation of pannus (proliferative granulation tissue A), which erodes articular cartilage and bone.
PREDISPOSING FACTORS	Age, female, obesity, joint trauma.	Female, HLA-DR4, smoking, silica exposure. ⊕ rheumatoid factor (IgM antibody that targets IgG Fc region; in 80%), anti-cyclic citrullinated peptide antibody (more specific).
PRESENTATION	Pain in weight-bearing joints after use (eg, at the end of the day), improving with rest. Asymmetric joint involvement. Knee cartilage loss begins medially ("bowlegged"). No systemic symptoms.	Pain, swelling, and morning stiffness lasting > 1 hour, improving with use. Symmetric joint involvement. Systemic symptoms (fever, fatigue, weight loss). Extraarticular manifestations common.*
JOINT FINDINGS	Osteophytes (bone spurs), joint space narrowing, subchondral sclerosis and cysts. Synovial fluid non-inflammatory (WBC $< 2000/\text{mm}^3$). Involves DIP (Heberden nodes B) and PIP (Bouchard nodes C), and 1st CMC; not MCP.	Erosions, juxta-articular osteopenia, soft tissue swelling, subchondral cysts, joint space narrowing. Deformities: cervical subluxation, ulnar finger deviation, swan neck D, boutonniere E. Involves MCP, PIP, wrist; not DIP or 1st CMC. Synovial fluid inflammatory.
TREATMENT	Acetaminophen, NSAIDs, intra-articular glucocorticoids.	NSAIDs, glucocorticoids, disease-modifying agents (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), biologic agents (eg, TNF-α inhibitors).

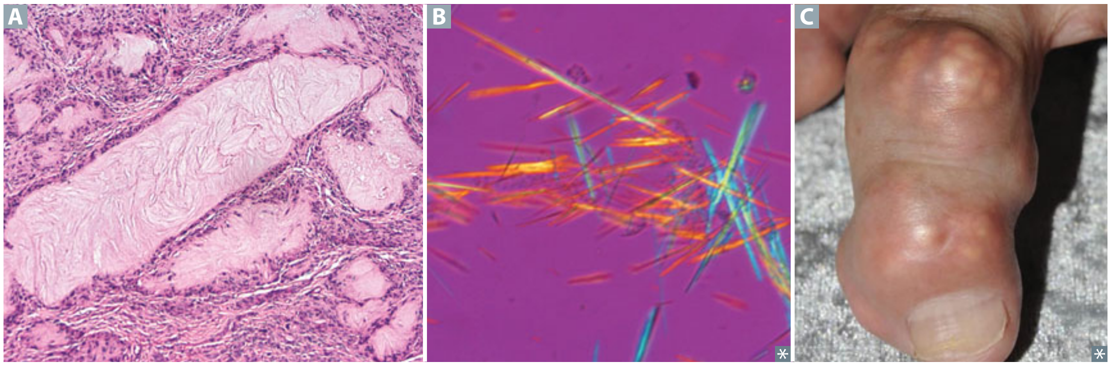
*Extraarticular manifestations include rheumatoid nodules (fibrinoid necrosis with palisading histiocytes) in subcutaneous tissue and lung (+ pneumoconiosis → Caplan syndrome), interstitial lung disease, pleuritis, pericarditis, anemia of chronic disease, neutropenia + splenomegaly (Felty syndrome), AA amyloidosis, Sjögren syndrome, scleritis, carpal tunnel syndrome.


Normal
Osteoarthritis
Joint capsule and synovial lining
Synovial cavity
Cartilage
Thickened capsule
Slight synovial hypertrophy
Osteophyte
Ulcerated cartilage
Sclerotic bone
Joint space narrowing
Subchondral bone cyst
Normal
Rheumatoid arthritis
Joint capsule and synovial lining
Synovial cavity
Cartilage
Bone and cartilage erosion
Increased synovial fluid
Pannus formation

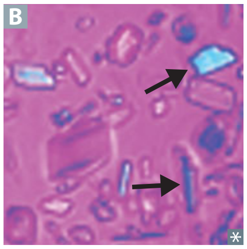


Gout

FINDINGS	Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints A. More common in males. Associated with hyperuricemia, which can be caused by: ▪ Underexcretion of uric acid (90% of patients)—largely idiopathic, potentiated by renal failure; can be exacerbated by certain medications (eg, thiazide diuretics). ▪ Overproduction of uric acid (10% of patients)—Lesch-Nyhan syndrome, PRPP excess, ↑ cell turnover (eg, tumor lysis syndrome), von Gierke disease. Crystals are needle shaped and ⊖ birefringent under polarized light (yellow under parallel light, blue under perpendicular light B).
SYMPTOMS	Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation C (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal with foods rich in purines (eg, red meat, seafood), trauma, surgery, dehydration, diuresis, or alcohol consumption (alcohol metabolites compete for same excretion sites in kidney as uric acid → ↓ uric acid secretion and subsequent buildup in blood).
TREATMENT	Acute: NSAIDs (eg, indomethacin), glucocorticoids, colchicine. Chronic (preventive): xanthine oxidase inhibitors (eg, allopurinol, febuxostat).



Calcium pyrophosphate deposition disease



Deposition of calcium pyrophosphate crystals within the joint space (arrows in A). Occurs in patients > 50 years old; both sexes affected equally. Usually idiopathic, sometimes associated with hemochromatosis, hyperparathyroidism, joint trauma.

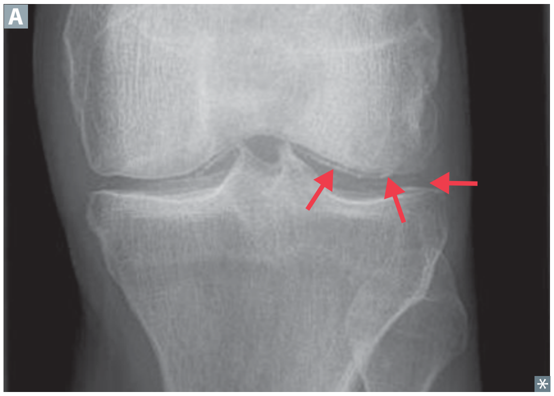
Pain and swelling with acute inflammation (pseudogout) and/or chronic degeneration (pseudo-osteoarthritis). Knee most commonly affected joint.

Chondrocalcinosis (cartilage calcification) on x-ray.

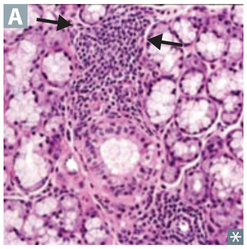
Crystals are rhomboid and weakly ⊕ birefringent under polarized light (blue when parallel to light) B.

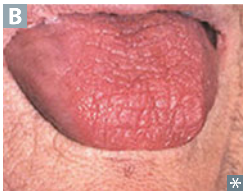
Acute treatment: NSAIDs, colchicine, glucocorticoids.

Prophylaxis: colchicine.



Sjögren syndrome





Autoimmune disorder characterized by destruction of exocrine glands (especially lacrimal and salivary) by lymphocytic infiltrates A. Predominantly affects females 40–60 years old.

Findings:

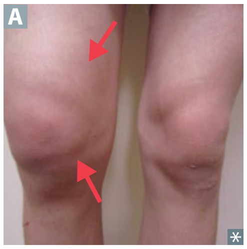
- Inflammatory joint pain
- Keratoconjunctivitis sicca (↓ tear production and subsequent corneal damage)
- Xerostomia (↓ saliva production B)
- Presence of antinuclear antibodies, rheumatoid factor (can be in the absence of rheumatoid arthritis), antiribonucleoprotein antibodies: SS-A (anti-Ro) and/or SS-B (anti-La)
- Bilateral parotid enlargement

A common 1° disorder or a 2° syndrome associated with other autoimmune disorders (eg, rheumatoid arthritis, SLE, systemic sclerosis).

Complications: dental caries; mucosa-associated lymphoid tissue (MALT) lymphoma (may present as parotid enlargement).

Labial salivary gland biopsy can confirm diagnosis.

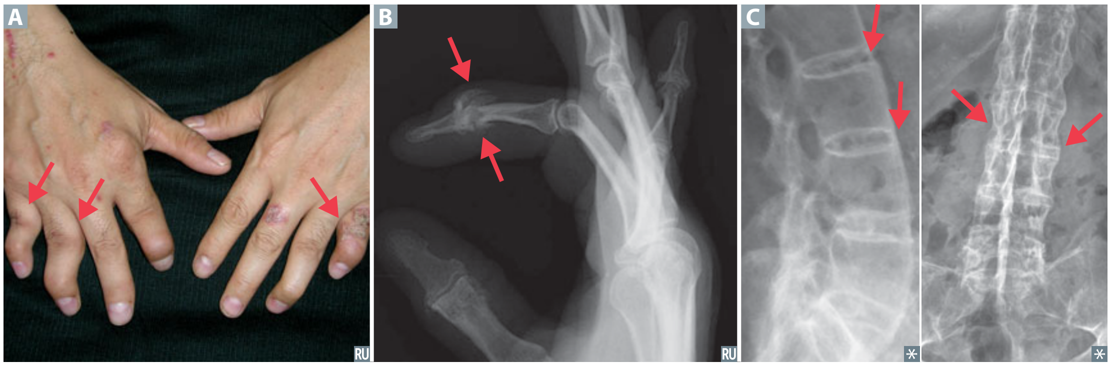
Septic arthritis



S aureus, *Streptococcus*, and *Neisseria gonorrhoeae* are common causes. Affected joint is swollen A, red, and painful. Synovial fluid purulent (WBC > 50,000/mm^3).

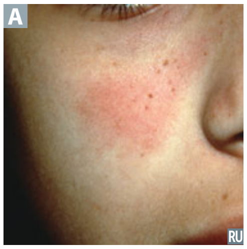
Gonococcal arthritis—STI that presents as either purulent arthritis (eg, knee) or triad of polyarthralgia, tenosynovitis (eg, hand), dermatitis (eg, pustules).

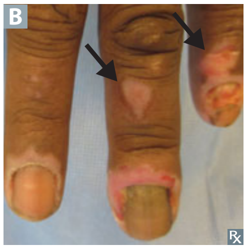
Seronegative spondyloarthritis	Arthritis without rheumatoid factor (no anti-IgG antibody). Strong association with HLA-B27 (MHC class I serotype). Subtypes (**PAIR**) share variable occurrence of inflammatory back pain (associated with morning stiffness, improves with exercise), peripheral arthritis, enthesitis (inflamed insertion sites of tendons, eg, Achilles), dactylitis ("sausage fingers"), uveitis.	
Psoriatic arthritis	Associated with skin psoriasis and nail lesions. Asymmetric and patchy involvement A. Dactylitis and "pencil-in-cup" deformity of DIP on x-ray B.	Seen in fewer than ⅓ of patients with psoriasis.
Ankylosing spondylitis	Symmetric involvement of spine and sacroiliac joints → ankylosis (joint fusion), uveitis, aortic regurgitation.	Bamboo spine (vertebral fusion) C. Can cause restrictive lung disease due to limited chest wall expansion (costovertebral and costosternal ankylosis). More common in males.
Inflammatory bowel disease	Crohn disease and ulcerative colitis are often associated with spondyloarthritis.	
Reactive arthritis	Formerly known as Reiter syndrome. Classic triad: ▪ **Conjunctivitis** ▪ **Urethritis** ▪ **Arthritis**	**"Can't see, can't pee, can't bend my knee."** *Shigella*, *Yersinia*, *Chlamydia*, *Campylobacter*, *Salmonella* (ShY ChiCS).



Systemic lupus erythematosus

SYMPTOMS





Classic presentation: rash, joint pain, and fever, most commonly in a female of reproductive age and African-American descent.

Libman-Sacks Endocarditis—nonbacterial, verrucous thrombi usually on mitral or aortic valve and can be present on either surface of the valve (but usually on undersurface) (**LSE** in **SLE**).

Lupus nephritis (glomerular deposition of anti-DNA immune complexes) can be nephritic or nephrotic (hematuria or proteinuria). Most common and severe type is diffuse proliferative.

Common causes of death in SLE:

- Cardiovascular disease
- Infections
- Renal disease

RASH OR PAIN:

- **R**ash (malar A or discoid B)
- **A**rthritis (nonerosive)
- **S**erositis
- **H**ematologic disorders (eg, cytopenias)
- **O**ral/nasopharyngeal ulcers
- **R**enal disease
- **P**hotosensitivity
- **A**ntinuclear antibodies
- **I**mmunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid)
- **N**eurologic disorders (eg, seizures, psychosis)

FINDINGS

Antinuclear antibodies (ANA)	Sensitive, not specific
Anti-dsDNA antibodies	Specific, poor prognosis (renal disease)
Anti-Smith antibodies	Specific, not prognostic (directed against snRNPs)
Antihistone antibodies	Sensitive for drug-induced lupus (eg, hydralazine, procainamide)
↓ C3, C4, and CH_{50} due to immune complex formation.	

TREATMENT

NSAIDs, steroids, immunosuppressants, hydroxychloroquine.

Antiphospholipid syndrome

1° or 2° autoimmune disorder (most commonly in SLE).

Diagnose based on clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion along with laboratory findings of lupus anticoagulant, anticardiolipin, anti-β_2 glycoprotein antibodies.

Treat with systemic anticoagulation.

Anticardiolipin antibodies can cause false-positive VDRL/RPR, and lupus anticoagulant can cause prolonged PTT, which is not corrected by the addition of normal platelet-free plasma.

Mixed connective tissue disease

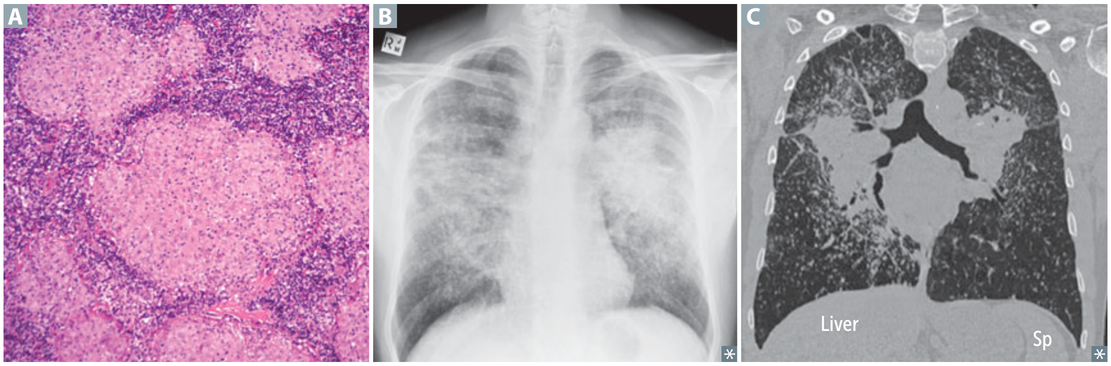
Features of SLE, systemic sclerosis, and/or polymyositis. Associated with anti-U1 RNP antibodies (speckled ANA).

Sarcoidosis

Characterized by immune-mediated, widespread noncaseating granulomas A, elevated serum ACE levels, and elevated CD4+/CD8+ ratio in bronchoalveolar lavage fluid. More common in African-American females. Often asymptomatic except for enlarged lymph nodes. Findings on CXR of bilateral adenopathy and coarse reticular opacities B; CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy C.

Associated with restrictive lung disease (interstitial fibrosis), erythema nodosum, lupus pernio (skin lesions on face resembling lupus), Bell palsy, epithelioid granulomas containing microscopic Schaumann and asteroid bodies, uveitis, hypercalcemia (due to ↑ 1α-hydroxylase–mediated vitamin D activation in macrophages).

Treatment: steroids (if symptomatic).



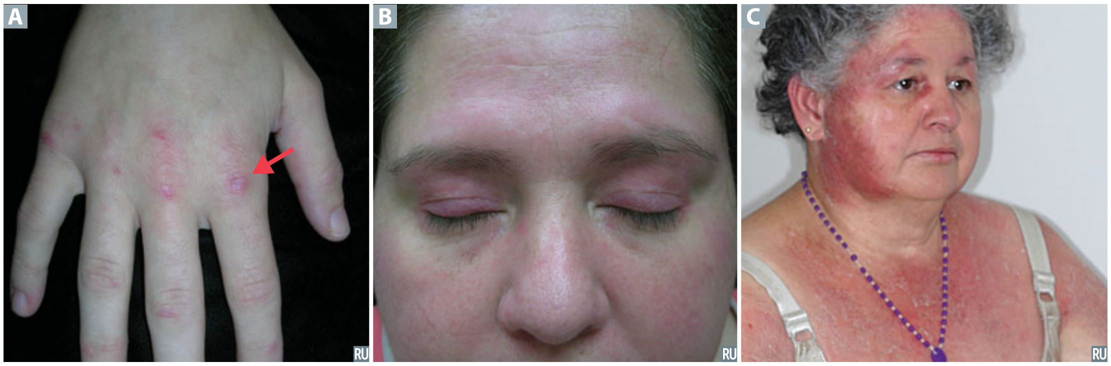
Polymyalgia rheumatica

SYMPTOMS	Pain and stiffness in shoulders and hips, often with fever, malaise, weight loss. Does not cause muscular weakness. More common in women > 50 years old; associated with giant cell (temporal) arteritis.
FINDINGS	↑ ESR, ↑ CRP, normal CK.
TREATMENT	Rapid response to low-dose corticosteroids.

Fibromyalgia

Most commonly seen in women 20–50 years old. Chronic, widespread musculoskeletal pain associated with “tender points,” stiffness, paresthesias, poor sleep, fatigue, cognitive disturbance (“fibro fog”). Treatment: regular exercise, antidepressants (TCAs, SNRIs), anticonvulsants.

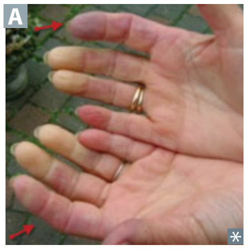
Polymyositis/ dermatomyositis	↑ CK, ⊕ ANA, ⊕ anti-Jo-1, ⊕ anti-SRP, ⊕ anti-Mi-2 antibodies. Treatment: steroids followed by long-term immunosuppressant therapy (eg, methotrexate).
Polymyositis	Progressive symmetric proximal muscle weakness, characterized by endomysial inflammation with CD8+ T cells. Most often involves shoulders.
Dermatomyositis	Similar to polymyositis, but also involves malar rash (similar to SLE), Gottron papules A, heliotrope (erythematous periorbital) rash B, "shawl and face" rash C, "mechanic's hands." ↑ risk of occult malignancy. Perimysial inflammation and atrophy with CD4+ T cells.



Neuromuscular junction diseases

	Myasthenia gravis	Lambert-Eaton myasthenic syndrome
FREQUENCY	Most common NMJ disorder	Uncommon
PATHOPHYSIOLOGY	Autoantibodies to postsynaptic ACh receptor	Autoantibodies to presynaptic Ca^{2+} channel → ↓ ACh release
CLINICAL	Ptosis, diplopia, weakness Worsens with muscle use Improvement after edrophonium (tensilon) test	Proximal muscle weakness, autonomic symptoms (dry mouth, impotence) Improves with muscle use
ASSOCIATED WITH	Thymoma, thymic hyperplasia	Small cell lung cancer
AChE INHIBITOR ADMINISTRATION	Reverses symptoms (edrophonium to diagnose, pyridostigmine to treat)	Minimal effect

Raynaud phenomenon

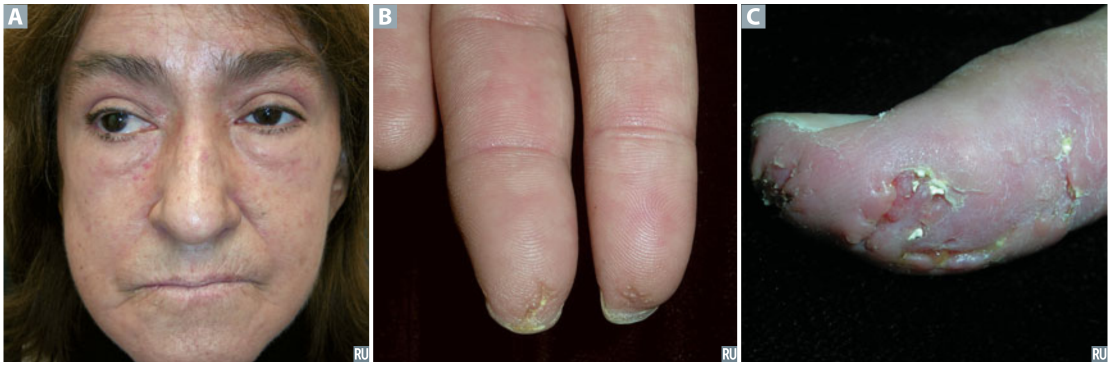


↓ blood flow to skin due to arteriolar (small vessel) vasospasm in response to cold or stress: color change from white (ischemia) to blue (hypoxia) to red (reperfusion). Most often in the fingers A and toes. Called Raynaud disease when 1° (idiopathic), Raynaud syndrome when 2° to a disease process such as mixed connective tissue disease, SLE, or CREST syndrome (limited form of systemic sclerosis). Digital ulceration (critical ischemia) seen in 2° Raynaud syndrome. Treat with Ca^{2+} channel blockers.

Scleroderma (systemic sclerosis)

Triad of autoimmunity, noninflammatory vasculopathy, and collagen deposition with fibrosis. Commonly sclerosis of skin, manifesting as puffy, taut skin A without wrinkles, fingertip pitting B. Also sclerosis of renal, pulmonary (most common cause of death), cardiovascular, GI systems. 75% female. 2 major types:

- **Diffuse scleroderma**—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody (anti-DNA topoisomerase I antibody).
- **Limited scleroderma**—limited skin involvement confined to fingers and face. Also with CREST syndrome: Calcinosis C, anti-Centromere antibody, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia. More benign clinical course.



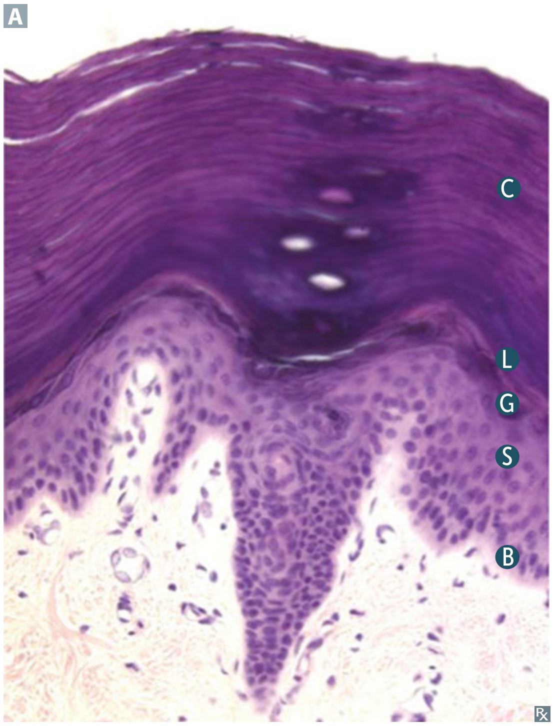
▶ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—DERMATOLOGY

Skin layers

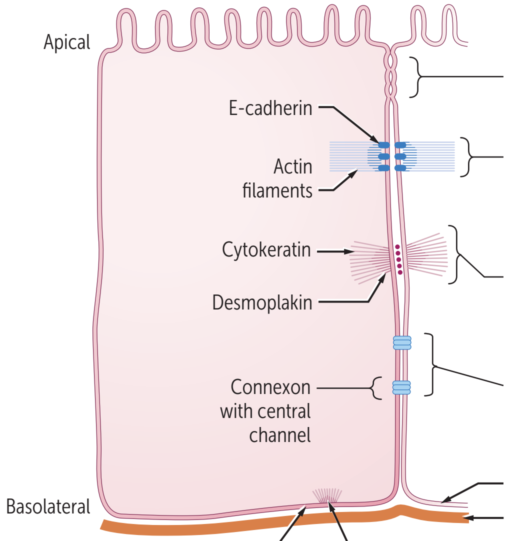
Skin has 3 layers: epidermis, dermis, subcutaneous fat (hypodermis, subcutis).
Epidermis layers from surface to base A:

- Stratum Corneum (keratin)
- Stratum Lucidum
- Stratum Granulosum
- Stratum Spinosum (desmosomes)
- Stratum Basale (stem cell site)

Californians Like Girls in String Bikinis.



Epithelial cell junctions



Tight junction (zonula occludens)—prevents paracellular movement of solutes; composed of claudins and occludins.

Adherens junction (belt desmosome, zonula adherens)—below tight junction, forms "belt" connecting actin cytoskeletons of adjacent cells with **CAD**herins (**Ca**$^{2+}$-dependent **ad**hesion proteins). Loss of E-cadherin promotes metastasis.

Desmosome (spot desmosome, macula adherens)—structural support via intermediate filament interactions. Autoantibodies → pemphigus vulgaris.

Gap junction—channel proteins called connexons permit electrical and chemical communication between cells.

Cell membrane

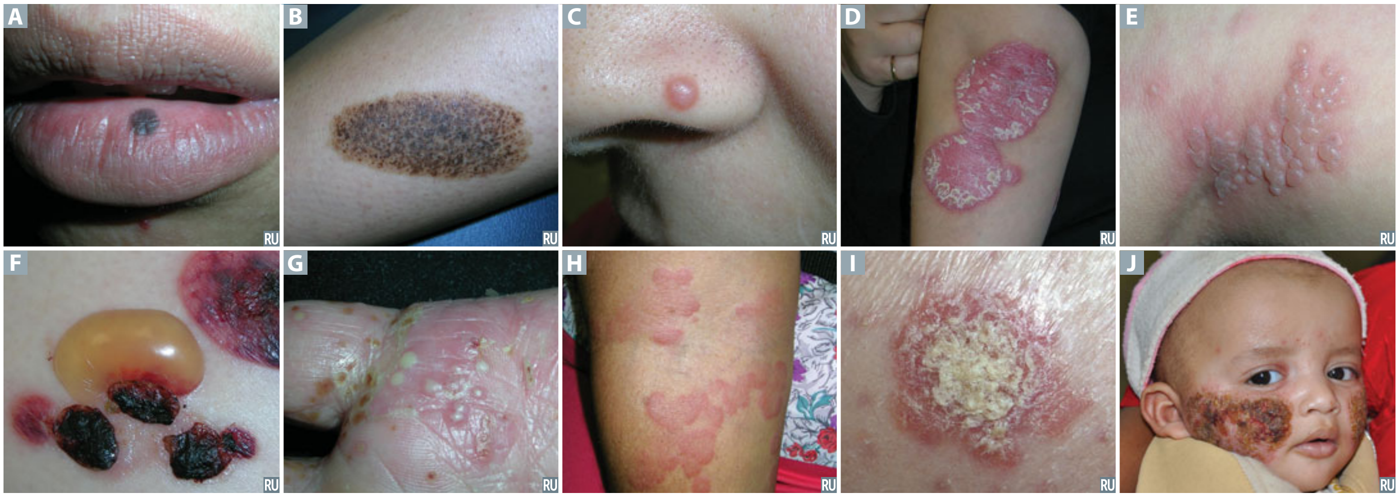
Basement membrane

Integrins—membrane proteins that maintain **integri**ty of basolateral membrane by binding to collagen and laminin in basement membrane.

Hemidesmosome—connects keratin in basal cells to underlying basement membrane. Autoantibodies → **bullo**us pemphigoid. (Hemidesmosomes are down "**bullo**w").

Dermatologic macroscopic terms (morphology)

LESION	CHARACTERISTICS	EXAMPLES
Macule	Flat lesion with well-circumscribed change in skin color < 1 cm	Freckle, labial macule A
Patch	Macule > 1 cm	Large birthmark (congenital nevus) B
Papule	Elevated solid skin lesion < 1 cm	Mole (nevus) C, acne
Plaque	Papule > 1 cm	Psoriasis D
Vesicle	Small fluid-containing blister < 1 cm	Chickenpox (varicella), shingles (zoster) E
Bulla	Large fluid-containing blister > 1 cm	Bullous pemphigoid F
Pustule	Vesicle containing pus	Pustular psoriasis G
Wheal	Transient smooth papule or plaque	Hives (urticaria) H
Scale	Flaking off of stratum corneum	Eczema, psoriasis, SCC I
Crust	Dry exudate	Impetigo J

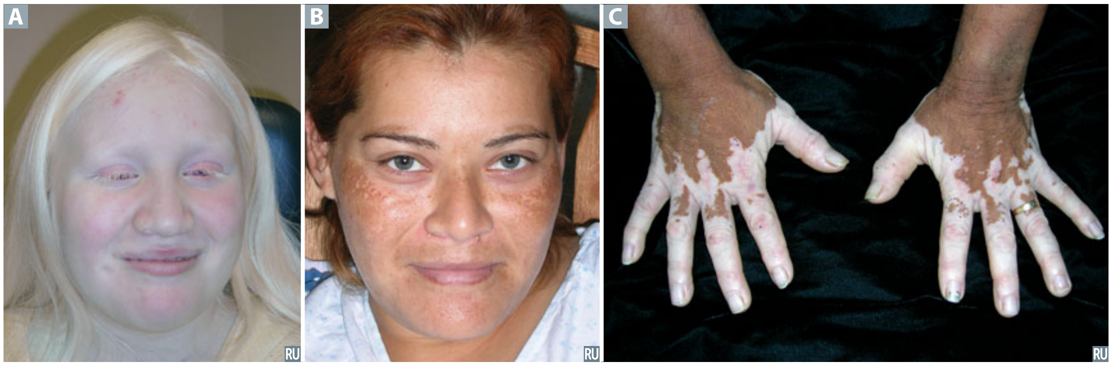


Dermatologic microscopic terms

LESION	CHARACTERISTICS	EXAMPLES
Hyperkeratosis	↑ thickness of stratum corneum	Psoriasis, calluses
Parakeratosis	Hyperkeratosis with retention of nuclei in stratum corneum	Psoriasis
Hypergranulosis	↑ thickness of stratum granulosum	Lichen planus
Spongiosis	Epidermal accumulation of edematous fluid in intercellular spaces	Eczematous dermatitis
Acantholysis	Separation of epidermal cells	Pemphigus vulgaris
Acanthosis	Epidermal hyperplasia (↑ spinosum)	Acanthosis nigricans

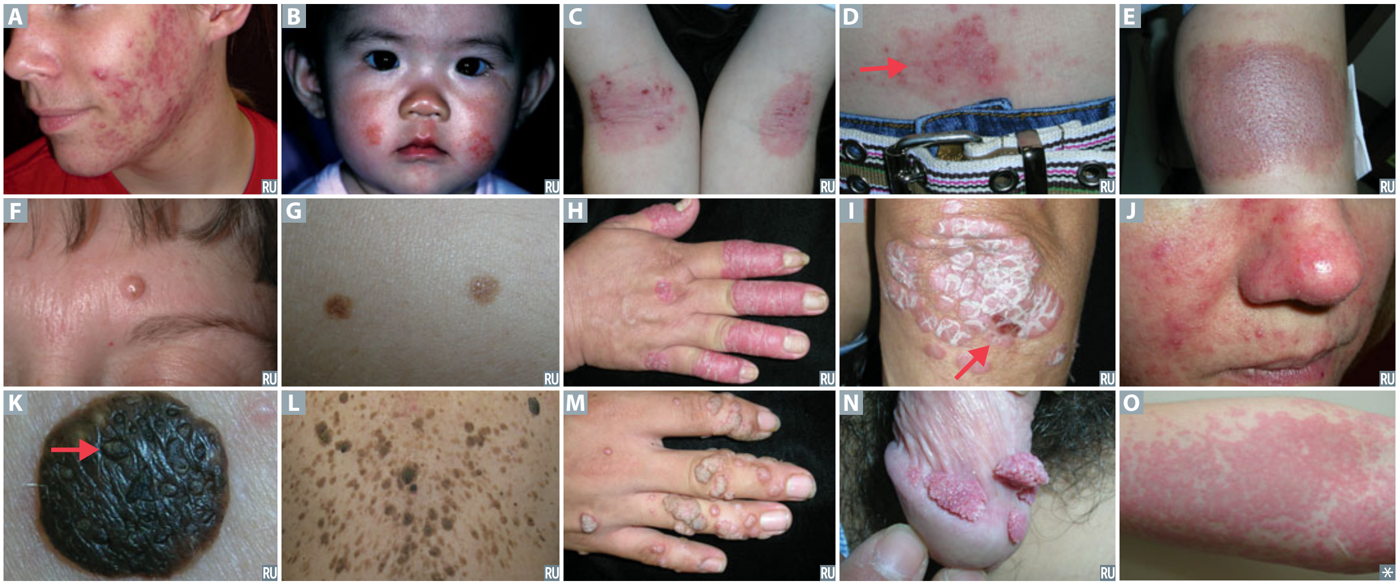
Pigmented skin disorders

Albinism	Normal melanocyte number with ↓ melanin production A due to ↓ tyrosinase activity or defective tyrosine transport. ↑ risk of skin cancer.
Melasma (chloasma)	Hyperpigmentation associated with pregnancy ("mask of pregnancy" B) or OCP use.
Vitiligo	Irregular areas of complete depigmentation C. Caused by autoimmune destruction of melanocytes.



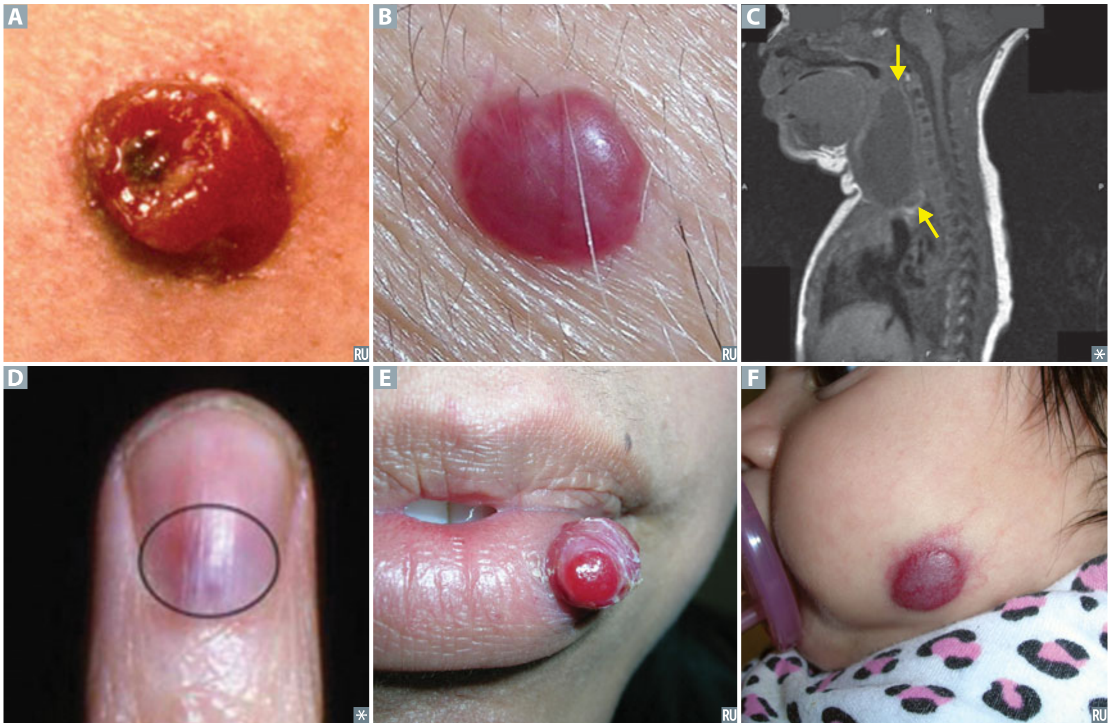
Common skin disorders

Acne	Multifactorial etiology—↑ sebum/androgen production, abnormal keratinocyte desquamation, *Propionibacterium acnes* colonization of the pilosebaceous unit (comedones), and inflammation (papules/pustules A, nodules, cysts). Treatment includes retinoids, benzoyl peroxide, and antibiotics.
Atopic dermatitis (eczema)	Pruritic eruption, commonly on skin flexures. Often associated with other atopic diseases (asthma, allergic rhinitis, food allergies); ↑ serum IgE. Usually appears on face in infancy B and then in antecubital fossa C in children and adults.
Allergic contact dermatitis	Type IV hypersensitivity reaction that follows exposure to allergen. Lesions occur at site of contact (eg, nickel D, poison ivy, neomycin E).
Melanocytic nevus	Common mole. Benign, but melanoma can arise in congenital or atypical moles. Intradermal nevi are papular F. Junctional nevi are flat macules G.
Pseudofolliculitis barbae	Foreign body inflammatory facial skin disorder characterized by firm, hyperpigmented papules and pustules that are painful and pruritic. Located on cheeks, jawline, and neck. Commonly occurs as a result of shaving (“razor bumps”), primarily affects African-American males.
Psoriasis	Papules and plaques with silvery scaling H, especially on knees and elbows. Acanthosis with parakeratotic scaling (nuclei still in stratum corneum), Munro microabscesses. ↑ stratum spinosum, ↓ stratum granulosum. Auspitz sign (arrow in I)—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Can be associated with nail pitting and psoriatic arthritis.
Rosacea	Inflammatory facial skin disorder characterized by erythematous papules and pustules J, but no comedones. May be associated with facial flushing in response to external stimuli (eg, alcohol, heat). Phymatous rosacea can cause rhinophyma (bulbous deformation of nose).
Seborrheic keratosis	Flat, greasy, pigmented squamous epithelial proliferation with keratin-filled cysts (horn cysts) K. Looks “stuck on.” Lesions occur on head, trunk, and extremities. Common benign neoplasm of older persons. Leser-Trélat sign L—sudden appearance of multiple seborrheic keratoses, indicating an underlying malignancy (eg, GI, lymphoid).
Verrucae	Warts; caused by HPV. Soft, tan-colored, cauliflower-like papules M. Epidermal hyperplasia, hyperkeratosis, koilocytosis. Condyloma acuminatum on genitals N.
Urticaria	Hives. Pruritic wheals that form after mast cell degranulation O. Characterized by superficial dermal edema and lymphatic channel dilation.



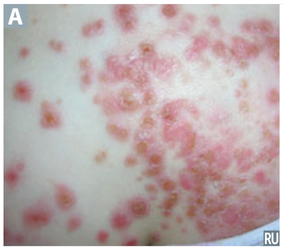
Vascular tumors of skin

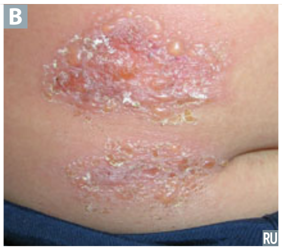
Angiosarcoma	Rare blood vessel malignancy typically occurring in the head, neck, and breast areas. Usually in elderly, on sun-exposed areas. Associated with radiation therapy and chronic postmastectomy lymphedema. Hepatic angiosarcoma associated with vinyl chloride and arsenic exposures. Very aggressive and difficult to resect due to delay in diagnosis.
Bacillary angiomatosis	Benign capillary skin papules A found in AIDS patients. Caused by *Bartonella henselae* infections. Frequently mistaken for Kaposi sarcoma, but has neutrophilic infiltrate.
Cherry hemangioma	Benign capillary hemangioma of the elderly B. Does not regress. Frequency ↑ with age.
Cystic hygroma	Cavernous lymphangioma of the neck C. Associated with Turner syndrome.
Glomus tumor	Benign, painful, red-blue tumor, commonly under fingernails D. Arises from modified smooth muscle cells of the thermoregulatory glomus body.
Kaposi sarcoma	Endothelial malignancy most commonly of the skin, but also mouth, GI tract, and respiratory tract. Associated with HHV-8 and HIV. Rarely mistaken for bacillary angiomatosis, but has lymphocytic infiltrate.
Pyogenic granuloma	Polypoid lobulated capillary hemangioma E that can ulcerate and bleed. Associated with trauma and pregnancy.
Strawberry hemangioma	Benign capillary hemangioma of infancy F. Appears in first few weeks of life (1/200 births); grows rapidly and regresses spontaneously by 5–8 years old.

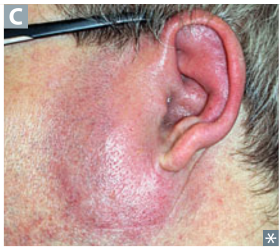


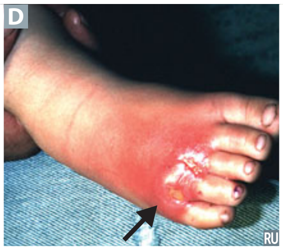
Skin infections

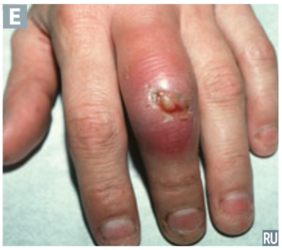
Bacterial infections	
Impetigo	Very superficial skin infection. Usually from *S aureus* or *S pyogenes*. Highly contagious. Honey-colored crusting A. Bullous impetigo B has bullae and is usually caused by *S aureus*.
Erysipelas	Infection involving upper dermis and superficial lymphatics, usually from *S pyogenes*. Presents with well-defined demarcation between infected and normal skin C.
Cellulitis	Acute, painful, spreading infection of deeper dermis and subcutaneous tissues. Usually from *S pyogenes* or *S aureus*. Often starts with a break in skin from trauma or another infection D.
Abscess	Collection of pus from a walled-off infection within deeper layers of skin E. Offending organism is almost always *S aureus*.
Necrotizing fasciitis	Deeper tissue injury, usually from anaerobic bacteria or *S pyogenes*. Pain may be out of proportion to exam findings. Results in crepitus from methane and CO_2 production. "Flesh-eating bacteria." Causes bullae and a purple color to the skin F.
Staphylococcal scalded skin syndrome	Exotoxin destroys keratinocyte attachments in stratum granulosum only (vs toxic epidermal necrolysis, which destroys epidermal-dermal junction). Characterized by fever and generalized erythematous rash with sloughing of the upper layers of the epidermis G that heals completely. ⊕ Nikolsky sign. Seen in newborns and children, adults with renal insufficiency.
Viral infections	
Herpes	Herpes virus infections (HSV1 and HSV2) of skin can occur anywhere from mucosal surfaces to normal skin. These include herpes labialis, herpes genitalis, herpetic whitlow H (finger).
Molluscum contagiosum	Umbilicated papules I caused by a poxvirus. While frequently seen in children, it may be sexually transmitted in adults.
Varicella zoster virus	Causes varicella (chickenpox) and zoster (shingles). Varicella presents with multiple crops of lesions in various stages from vesicles to crusts. Zoster is a reactivation of the virus in dermatomal distribution (unless it is disseminated).
Hairy leukoplakia	Irregular, white, painless plaques on lateral tongue that cannot be scraped off J. EBV mediated. Occurs in HIV-positive patients, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous).

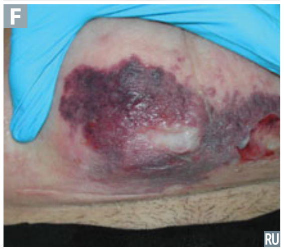


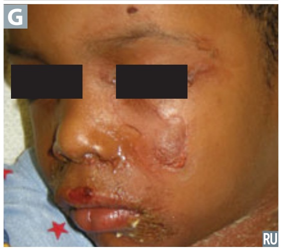


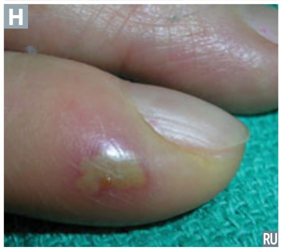


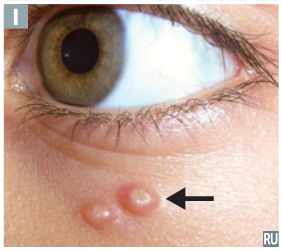


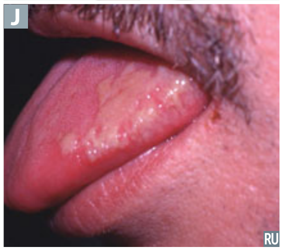






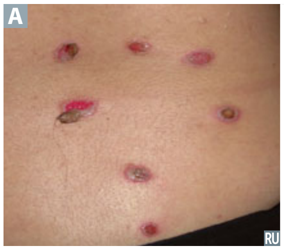


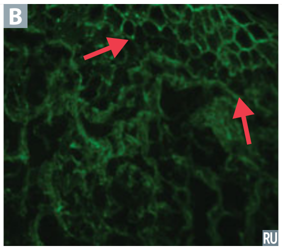


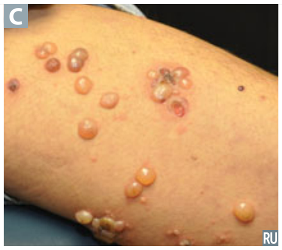


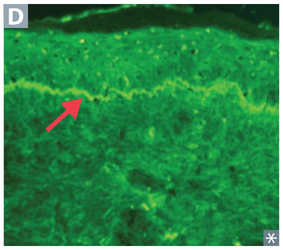
Blistering skin disorders

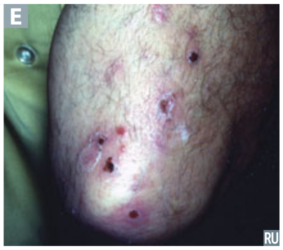
Pemphigus vulgaris	Potentially fatal autoimmune skin disorder with IgG antibody against desmoglein (component of desmosomes, which connect keratinocytes in the stratum spinosum). Flaccid intraepidermal bullae A caused by acantholysis (separation of keratinocytes, resembling a "row of tombstones"); oral mucosa is also involved. Type II hypersensitivity reaction. Immunofluorescence reveals antibodies around epidermal cells in a reticular (net-like) pattern B. Nikolsky sign ⊕ (separation of epidermis upon manual stroking of skin).
Bullous pemphigoid	Less severe than pemphigus vulgaris. Involves IgG antibody against hemidesmosomes (epidermal basement membrane; antibodies are "bullow" the epidermis). Tense blisters C containing eosinophils affect skin but spare oral mucosa. Immunofluorescence reveals linear pattern at epidermal-dermal junction D. Nikolsky sign ⊖.
Dermatitis herpetiformis	Pruritic papules, vesicles, and bullae (often found on elbows) E. Deposits of IgA at tips of dermal papillae. Associated with celiac disease. Treatment: dapsone, gluten-free diet.
Erythema multiforme	Associated with infections (eg, *Mycoplasma pneumoniae*, HSV), drugs (eg, sulfa drugs, β-lactams, phenytoin), cancers, autoimmune disease. Presents with multiple types of lesions—macules, papules, vesicles, target lesions (look like targets with multiple rings and dusky center showing epithelial disruption) F.
Stevens-Johnson syndrome	Characterized by fever, bullae formation and necrosis, sloughing of skin at dermal-epidermal junction, high mortality rate. Typically 2 mucous membranes are involved G H, and targetoid skin lesions may appear, as seen in erythema multiforme. Usually associated with adverse drug reaction. A more severe form of Stevens-Johnson syndrome (SJS) with > 30% of the body surface area involved is toxic epidermal necrolysis I J (TEN). 10–30% involvement denotes SJS-TEN.

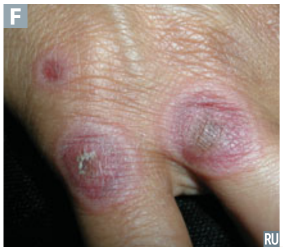


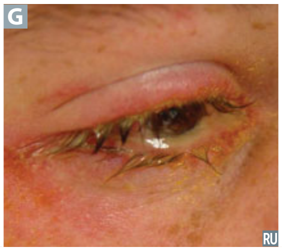


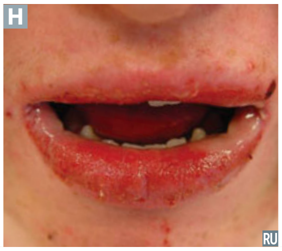


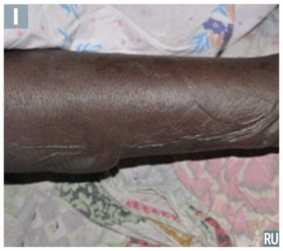


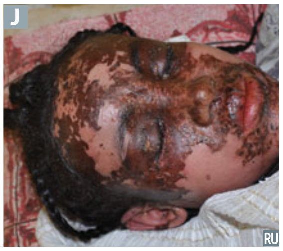






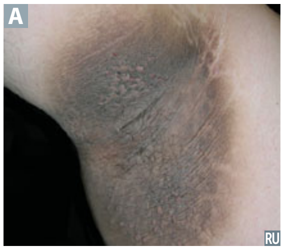


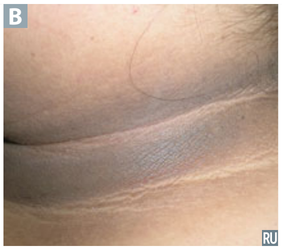


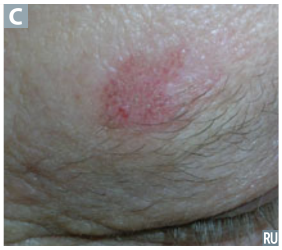


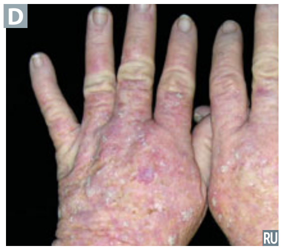
Miscellaneous skin disorders

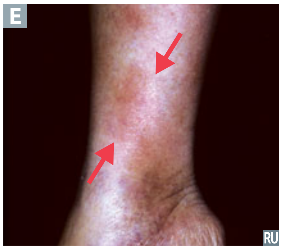
Acanthosis nigricans	Epidermal hyperplasia causing symmetric, hyperpigmented thickening of skin, especially in axilla or on neck A B. Associated with insulin resistance (eg, diabetes, obesity, Cushing syndrome), visceral malignancy (eg, gastric adenocarcinoma).
Actinic keratosis	Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules or plaques C D. Risk of squamous cell carcinoma is proportional to degree of epithelial dysplasia.
Erythema nodosum	Painful, raised inflammatory lesions of subcutaneous fat (panniculitis), usually on anterior shins. Often idiopathic, but can be associated with sarcoidosis, coccidioidomycosis, histoplasmosis, TB, streptococcal infections E, leprosy F, inflammatory bowel disease.
Lichen Planus	Pruritic, Purple, Polygonal Planar Papules and Plaques are the 6 P's of lichen Planus G H. Mucosal involvement manifests as Wickham striae (reticular white lines) and hypergranulosis. Sawtooth infiltrate of lymphocytes at dermal-epidermal junction. Associated with hepatitis C.
Pityriasis rosea	"Herald patch" I followed days later by other scaly erythematous plaques, often in a "Christmas tree" distribution on trunk J. Multiple plaques with collarette scale. Self-resolving in 6–8 weeks.
Sunburn	Acute cutaneous inflammatory reaction due to excessive UV irradiation. Causes DNA mutations, inducing apoptosis of keratinocytes. UVB is dominant in sunBurn, UVA in tAnning and photoAging. Exposure to UVA and UVB ↑ risk of skin cancer (basal cell carcinoma, squamous cell carcinoma, melanoma). Can also lead to impetigo.

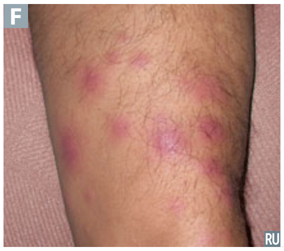


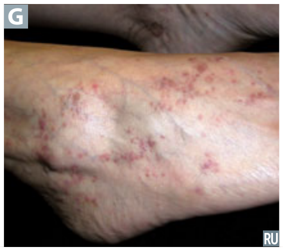


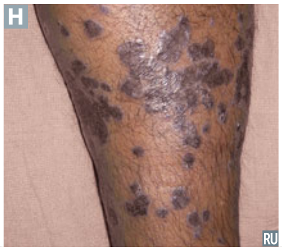


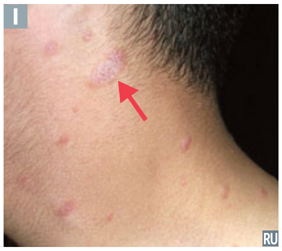


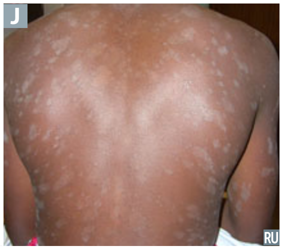




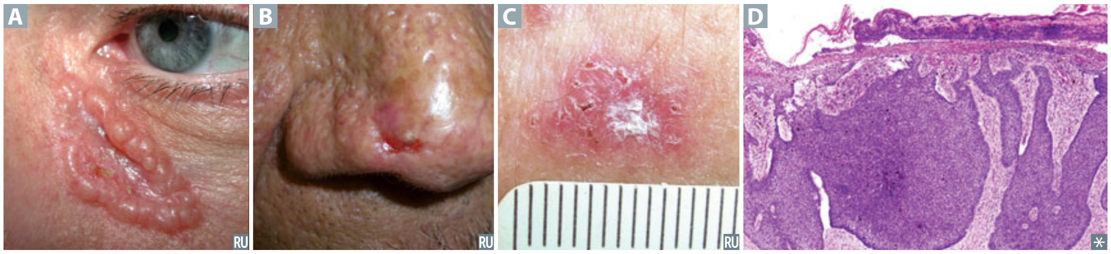
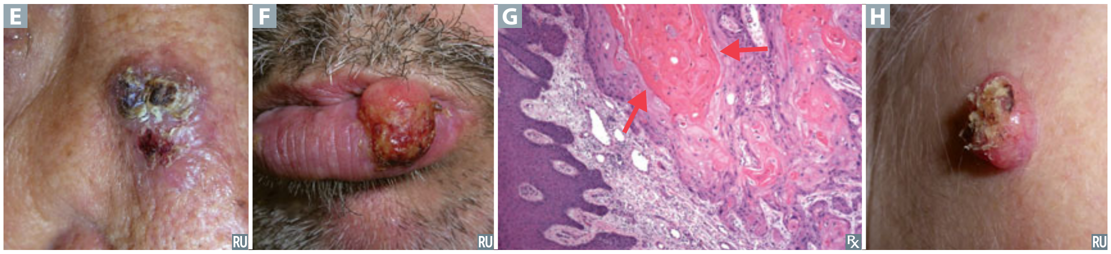
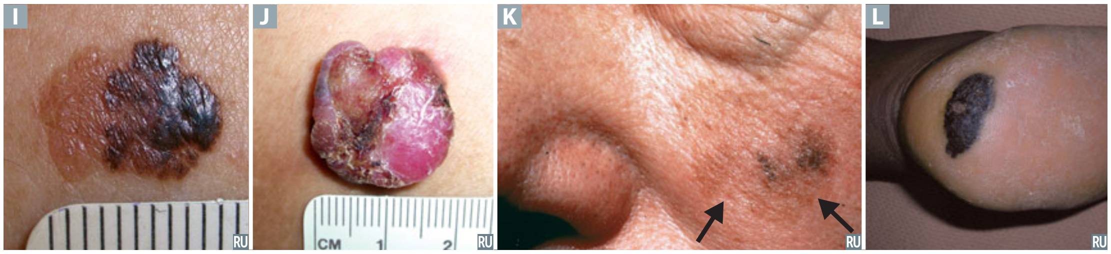






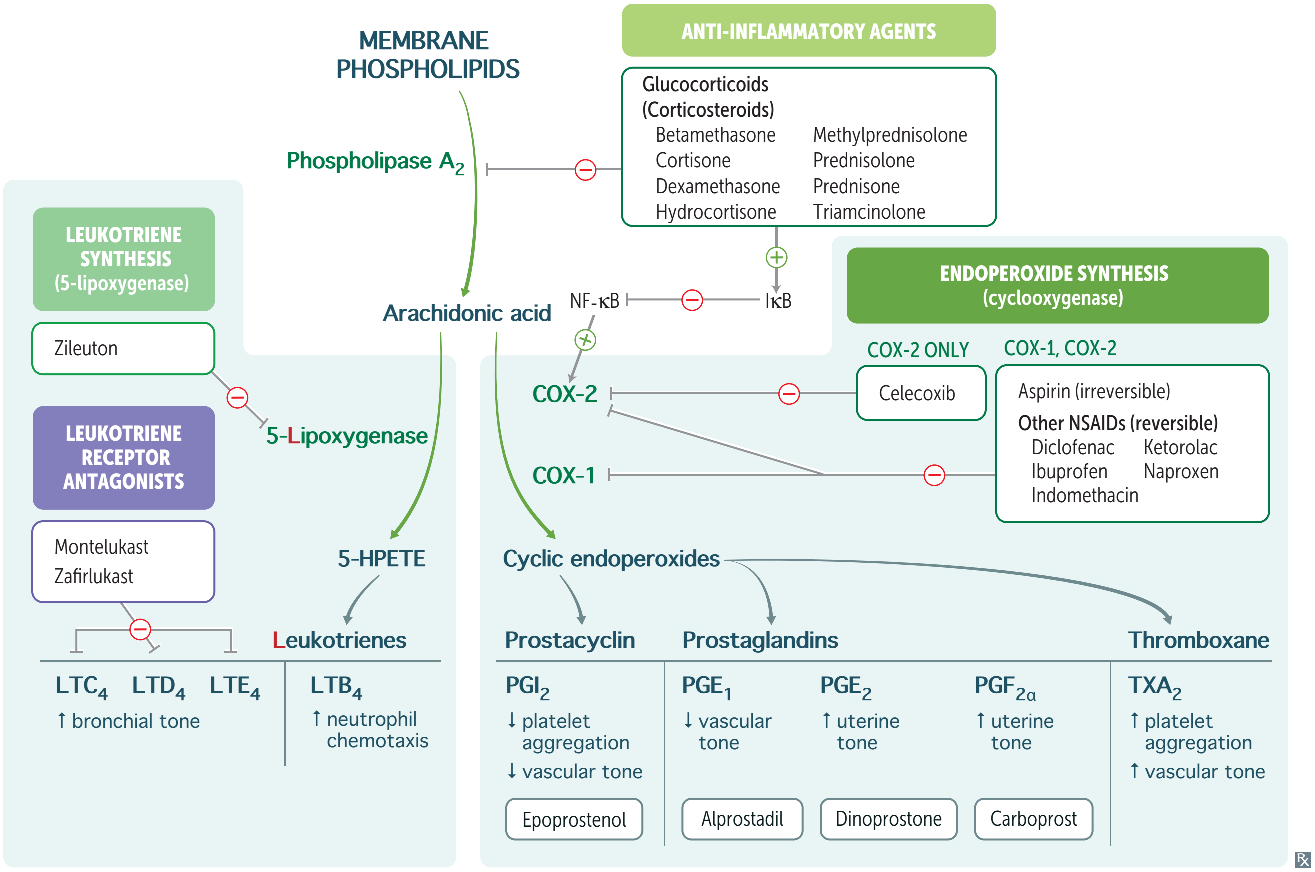


Skin cancer

Basal cell carcinoma	Most common skin cancer. Found in sun-exposed areas of body (eg, face). Locally invasive, but rarely metastasizes. Waxy, pink, pearly nodules, commonly with telangiectasias, rolled borders, central crusting or ulceration A. BCCs also appear as nonhealing ulcers with infiltrating growth B or as a scaling plaque (superficial BCC) C. Basal cell tumors have "palisading" nuclei D. 
Squamous cell carcinoma	Second most common skin cancer. Associated with excessive exposure to sunlight, immunosuppression, chronically draining sinuses, and occasionally arsenic exposure. Commonly appears on face E, lower lip F, ears, hands. Locally invasive, may spread to lymph nodes, and will rarely metastasize. Ulcerative red lesions with frequent scale. Histopathology: keratin "pearls" G. Actinic keratosis, a scaly plaque, is a precursor to squamous cell carcinoma. Keratoacanthoma is a variant that grows rapidly (4–6 weeks) and may regress spontaneously over months H. 
Melanoma	Common tumor with significant risk of metastasis. S-100 tumor marker. Associated with sunlight exposure and dysplastic nevi; fair-skinned persons are at ↑ risk. Depth of tumor (Breslow thickness) correlates with risk of metastasis. Look for the ABCDEs: Asymmetry, Border irregularity, Color variation, Diameter > 6 mm, and Evolution over time. At least 4 different types of melanoma, including superficial spreading I, nodular J, lentigo maligna K, and acral lentiginous L. Often driven by activating mutation in BRAF kinase. Primary treatment is excision with appropriately wide margins. Metastatic or unresectable melanoma in patients with *BRAF* V600E mutation may benefit from vemurafenib, a BRAF kinase inhibitor. 

▶ MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE—PHARMACOLOGY

Arachidonic acid pathway


MEMBRANE PHOSPHOLIPIDS
ANTI-INFLAMMATORY AGENTS
Glucocorticoids (Corticosteroids)
Betamethasone
Cortisone
Dexamethasone
Hydrocortisone
Methylprednisolone
Prednisolone
Prednisone
Triamcinolone
Phospholipase A2
LEUKOTRIENE SYNTHESIS (5-lipoxygenase)
Zileuton
Arachidonic acid
NF-κB
IκB
ENDOPEROXIDE SYNTHESIS (cyclooxygenase)
COX-2 ONLY
COX-1, COX-2
Celecoxib
Aspirin (irreversible)
Other NSAIDs (reversible)
Diclofenac
Ketorolac
Ibuprofen
Naproxen
Indomethacin
COX-2
COX-1
LEUKOTRIENE RECEPTOR ANTAGONISTS
Montelukast
Zafirlukast
5-Lipoxygenase
5-HPETE
Cyclic endoperoxides
Leukotrienes
Prostacyclin
Prostaglandins
Thromboxane
LTC4 LTD4 LTE4
↑ bronchial tone
LTB4
↑ neutrophil chemotaxis
PGI2
↓ platelet aggregation
↓ vascular tone
PGE1
↓ vascular tone
PGE2
↑ uterine tone
PGF2α
↑ uterine tone
TXA2
↑ platelet aggregation
↑ vascular tone
Epoprostenol
Alprostadil
Dinoprostone
Carboprost
℞

LTB_4 is a **neutrophil** chemotactic agent.	**N**eutrophils arrive "**B4**" others.
PGI_2 inhibits platelet aggregation and promotes vasodilation.	**P**latelet-**G**athering **I**nhibitor.

Acetaminophen

MECHANISM	Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.
CLINICAL USE	Antipyretic, analgesic, but not anti-inflammatory. Used instead of aspirin to avoid Reye syndrome in children with viral infection.
ADVERSE EFFECTS	Overdose produces hepatic necrosis; acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. N-acetylcysteine is antidote—regenerates glutathione.

Aspirin

MECHANISM	NSAID that irreversibly inhibits cyclooxygenase (both COX-1 and COX-2) by covalent acetylation → ↓ synthesis of TXA_2 and prostaglandins. ↑ bleeding time. No effect on PT, PTT. Effect lasts until new platelets are produced.
CLINICAL USE	Low dose (< 300 mg/day): ↓ platelet aggregation. Intermediate dose (300–2400 mg/day): antipyretic and analgesic. High dose (2400–4000 mg/day): anti-inflammatory.
ADVERSE EFFECTS	Gastric ulceration, tinnitus (CN VIII). Chronic use can lead to acute renal failure, interstitial nephritis, GI bleeding. Risk of Reye syndrome in children treated with aspirin for viral infection. Toxic doses cause respiratory alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis.

Celecoxib

MECHANISM	Reversibly and **sele**ctively inhibits the cyclooxygenase (**COX**) isoform 2 (“**Selecox**ib”), which is found in inflammatory cells and vascular endothelium and mediates inflammation and pain; spares COX-1, which helps maintain gastric mucosa. Thus, does not have the corrosive effects of other NSAIDs on the GI lining. Spares platelet function as TXA_2 production is dependent on COX-1.
CLINICAL USE	Rheumatoid arthritis, osteoarthritis.
ADVERSE EFFECTS	↑ risk of thrombosis. Sulfa allergy.

Nonsteroidal anti-inflammatory drugs

Ibuprofen, naproxen, indomethacin, ketorolac, diclofenac, meloxicam, piroxicam.

MECHANISM	Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). Block prostaglandin synthesis.
CLINICAL USE	Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a PDA.
ADVERSE EFFECTS	Interstitial nephritis, gastric ulcer (prostaglandins protect gastric mucosa), renal ischemia (prostaglandins vasodilate afferent arteriole), aplastic anemia.

Leflunomide

MECHANISM	Reversibly inhibits dihydroorotate dehydrogenase, preventing pyrimidine synthesis. Suppresses T-cell proliferation.
CLINICAL USE	Rheumatoid arthritis, psoriatic arthritis.
ADVERSE EFFECTS	Diarrhea, hypertension, hepatotoxicity, teratogenicity.

Bisphosphonates

Alendronate, ibandronate, risedronate, zoledronate.

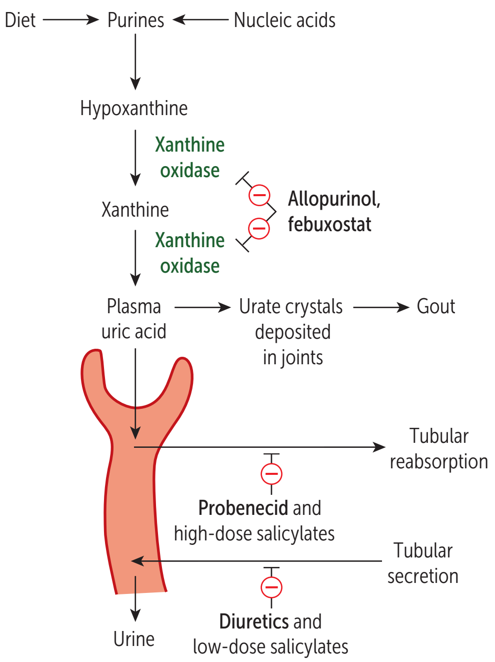
MECHANISM	Pyrophosphate analogs; bind hydroxyapatite in bone, inhibiting osteoclast activity.
CLINICAL USE	Osteoporosis, hypercalcemia, Paget disease of bone, metastatic bone disease, osteogenesis imperfecta.
ADVERSE EFFECTS	Esophagitis (if taken orally, patients are advised to take with water and remain upright for 30 minutes), osteonecrosis of jaw, atypical stress fractures.

Teriparatide

MECHANISM	Recombinant PTH analog given subcutaneously daily. ↑ osteoblastic activity.
CLINICAL USE	Osteoporosis. Causes ↑ bone growth compared to antiresorptive therapies (eg, bisphosphonates).
ADVERSE EFFECTS	↑ risk of osteosarcoma (avoid use in patients with Paget disease of the bone or unexplained elevation of alkaline phosphatase). Avoid in patients who have had prior cancers or radiation therapy. Transient hypercalcemia.

Gout drugs

Chronic gout drugs (preventive)	
Allopurinol	Competitive inhibitor of xanthine oxidase. ↓ conversion of hypoxanthine and xanthine to urate. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. ↑ concentrations of azathioprine and 6-MP (both normally metabolized by xanthine oxidase).
Febuxostat	Inhibits xanthine oxidase.
Pegloticase	Recombinant uricase that catalyzes metabolism of uric acid to allantoin (a more water-soluble product).
Probenecid	Inhibits reabsorption of uric acid in proximal convoluted tubule (also inhibits secretion of penicillin). Can precipitate uric acid calculi.
Acute gout drugs	
NSAIDs	Any full-dose NSAID (eg, naproxen, indomethacin). Avoid salicylates (may decrease uric acid excretion, particularly at low doses).
Glucocorticoids	Oral, intra-articular, or parenteral.
Colchicine	Binds and stabilizes tubulin to inhibit microtubule polymerization, impairing neutrophil chemotaxis and degranulation. Acute and prophylactic value. GI side effects.


Diet
Purines
Nucleic acids
Hypoxanthine
Xanthine oxidase
Xanthine
Xanthine oxidase
Allopurinol, febuxostat
Plasma uric acid
Urate crystals deposited in joints
Gout
Tubular reabsorption
Probenecid and high-dose salicylates
Tubular secretion
Diuretics and low-dose salicylates
Urine

TNF-α inhibitors

All TNF-α inhibitors predispose to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization.

DRUG	MECHANISM	CLINICAL USE
Etanercept	Fusion protein (receptor for TNF-α + IgG_1 Fc), produced by recombinant DNA. Etanercept intercepts TNF.	Rheumatoid arthritis, psoriasis, ankylosing spondylitis
Infliximab, adalimumab, certolizumab, golimumab	Anti-TNF-α monoclonal antibody.	Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis

NOTES

HIGH-YIELD SYSTEMS

Neurology and Special Senses

"*Estimated amount of glucose used by an adult human brain each day, expressed in M&Ms: 250.*"

—Harper's Index

"*Anything's possible if you've got enough nerve.*"

—J.K. Rowling, *Harry Potter and the Order of the Phoenix*

"*I like nonsense; it wakes up the brain cells.*"

—Dr. Seuss

"*I believe in an open mind, but not so open that your brains fall out.*"

—Arthur Hays Sulzberger

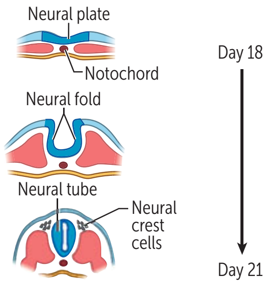
"*The chief function of the body is to carry the brain around.*"

—Thomas Edison

- Embryology 460
- Anatomy and Physiology 463
- Neuropathology 481
- Otology 503
- Ophthalmology 504
- Pharmacology 514

▶ NEUROLOGY—EMBRYOLOGY

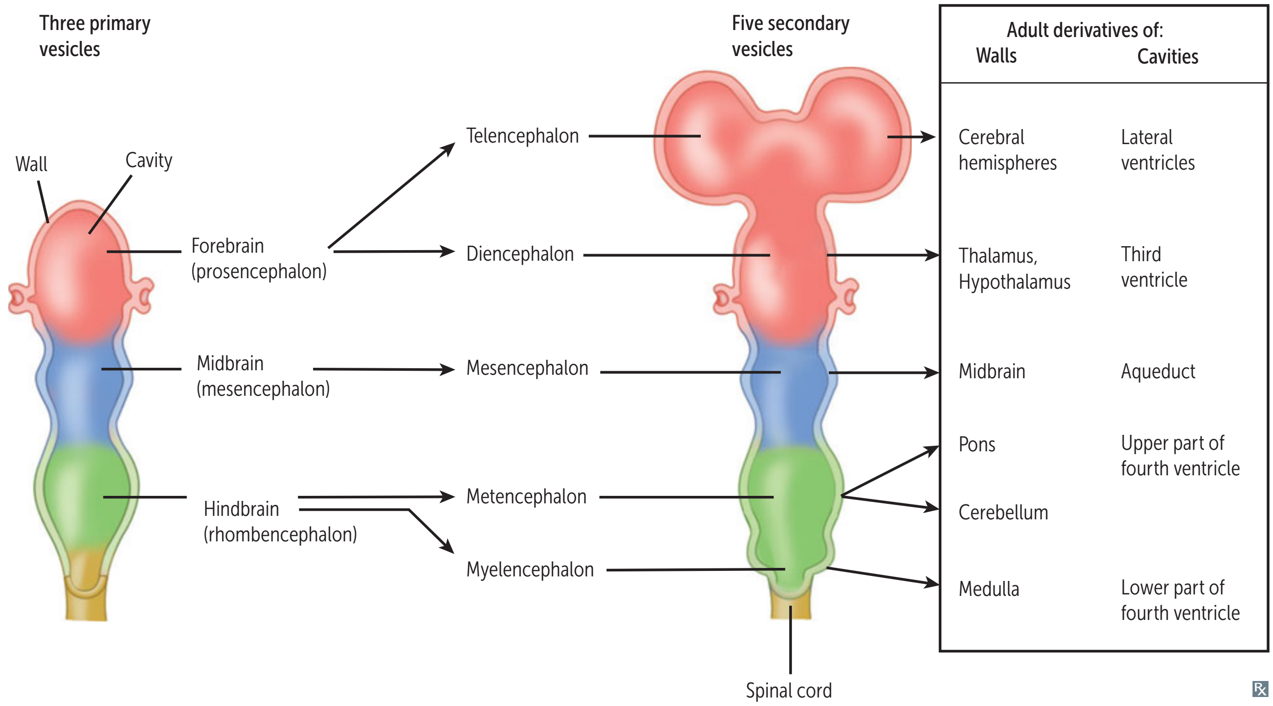
Neural development


Neural plate
Notochord
Neural fold
Neural tube
Neural crest cells
Day 18
Day 21

Notochord induces overlying ectoderm to differentiate into neuroectoderm and form neural plate.
Neural plate gives rise to neural tube and neural crest cells.
Notochord becomes nucleus pulposus of intervertebral disc in adults.

Alar plate (dorsal): sensory
Basal plate (ventral): motor
] Same orientation as spinal cord.

Regional specification of developing brain


Three primary vesicles
Wall
Cavity
Forebrain (prosencephalon)
Midbrain (mesencephalon)
Hindbrain (rhombencephalon)
Telencephalon
Diencephalon
Mesencephalon
Metencephalon
Myelencephalon
Five secondary vesicles
Spinal cord

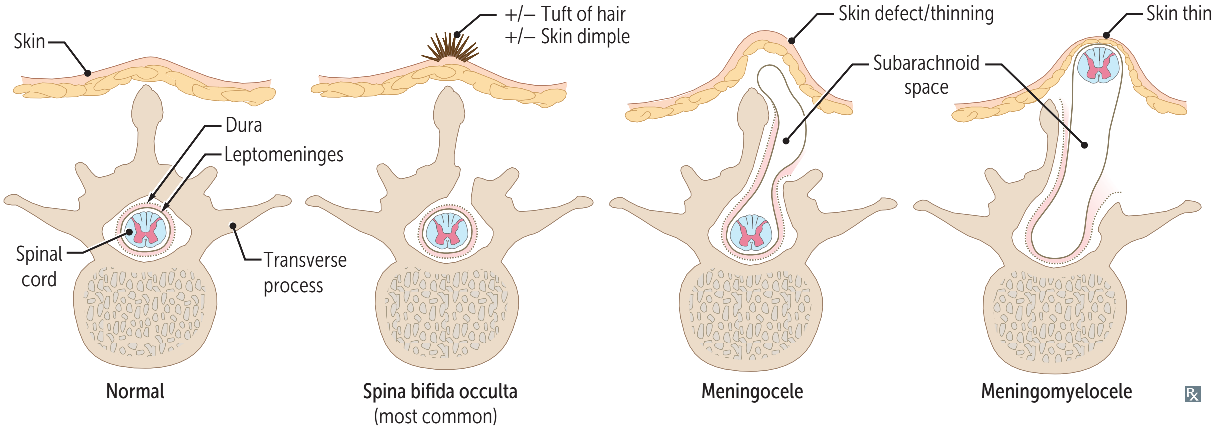
Adult derivatives of:

Walls	Cavities
Cerebral hemispheres	Lateral ventricles
Thalamus, Hypothalamus	Third ventricle
Midbrain	Aqueduct
Pons	Upper part of fourth ventricle
Cerebellum	
Medulla	Lower part of fourth ventricle

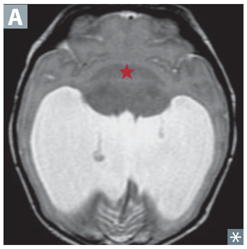
Central and peripheral nervous systems origins

Neuroepithelia in neural tube—CNS neurons, ependymal cells (inner lining of ventricles, make CSF), oligodendrocytes, astrocytes.
Neural crest—PNS neurons, Schwann cells.
Mesoderm—**M**icroglia (like **M**acrophages).

Neural tube defects	Neuropores fail to fuse (4th week) → persistent connection between amniotic cavity and spinal canal. Associated with maternal diabetes as well as low folic acid intake before conception and during pregnancy. ↑ α-fetoprotein (AFP) in amniotic fluid and maternal serum (except spina bifida occulta = normal AFP). ↑ acetylcholinesterase (AChE) in amniotic fluid is a helpful confirmatory test (fetal AChE in CSF flows through defect into amniotic fluid).
Anencephaly	Failure of rostral neuropore to close → no forebrain, open calvarium. Clinical findings: polyhydramnios (no swallowing center in brain).
Spina bifida occulta	Failure of caudal neuropore to close, but no herniation. Usually seen at lower vertebral levels. Dura is intact. Associated with tuft of hair or skin dimple at level of bony defect.
Meningocele	Meninges (but no neural tissue) herniate through bony defect. Associated with spina bifida cystica.
Meningomyelocele	Meninges and neural tissue (eg, cauda equina) herniate through bony defect.

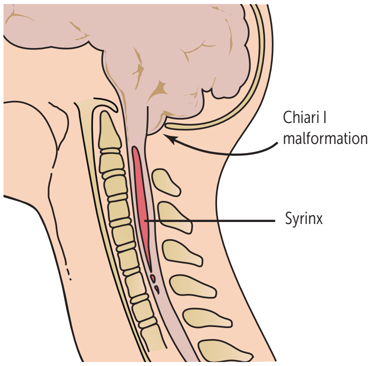

Skin
Dura
Leptomeninges
Spinal cord
Transverse process
+/– Tuft of hair
+/– Skin dimple
Skin defect/thinning
Subarachnoid space
Skin thin or absent
Normal
Spina bifida occulta
(most common)
Meningocele
Meningomyelocele

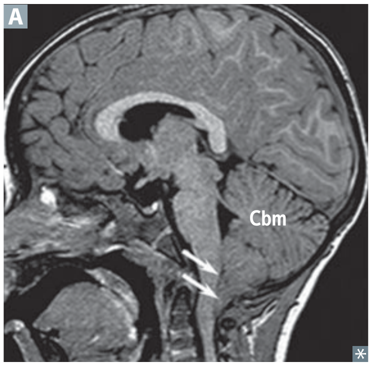
Holoprosencephaly	Failure of left and right hemispheres to separate; usually occurs during weeks 5–6. May be related to mutations in sonic hedgehog signaling pathway. Moderate form has cleft lip/palate, most severe form results in cyclopia. Seen in trisomy 13 and fetal alcohol syndrome. MRI A reveals monoventricle and fusion of basal ganglia (star in A).

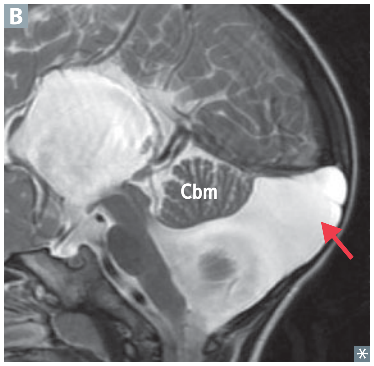


Posterior fossa malformations

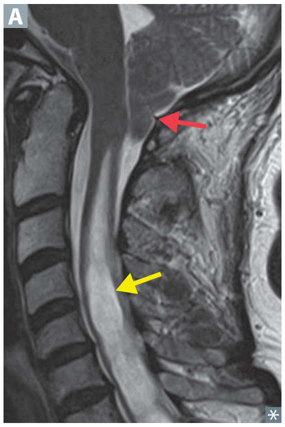
Chiari I malformation	Ectopia of cerebellar **tonsils** (1 structure) > 3–5 mm A. Congenital, usually asymptomatic in childhood, manifests in adulthood with headaches and cerebellar symptoms. Associated with spinal cavitations (eg, syringomyelia).
Chiari II malformation	Herniation of low-lying cerebellar **vermis** and **tonsils** (2 structures) through foramen magnum with aqueductal stenosis → hydrocephalus. Usually associated with lumbosacral meningomyelocele (may present as paralysis/sensory loss at and below the level of the lesion).
Dandy-Walker syndrome	Agenesis of cerebellar vermis with cystic enlargement of 4th ventricle (arrow in B), fills the enlarged posterior fossa. Associated with noncommunicating hydrocephalus, spina bifida.







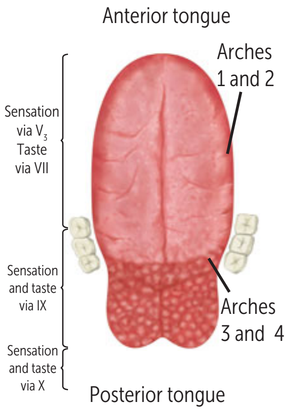
Syringomyelia



Cystic cavity (syrinx) within central canal of spinal cord (yellow arrow in A). Fibers crossing in anterior white commissure (spinothalamic tract) are typically damaged first. Results in a "cape-like," bilateral loss of pain and temperature sensation in upper extremities (fine touch sensation is preserved). Associated with Chiari malformations (red arrow shows low-lying cerebellar tonsils in A), trauma, and tumors.

Syrinx = tube, as in syringe.
Most common at C8–T1.

Tongue development


Anterior tongue
Arches 1 and 2
Sensation via V_3 Taste via VII
Sensation and taste via IX
Sensation and taste via X
Arches 3 and 4
Posterior tongue

1st and 2nd branchial arches form anterior $^{2}/_{3}$ (thus sensation via CN V_3, taste via CN VII).
3rd and 4th branchial arches form posterior $^{1}/_{3}$ (thus sensation and taste mainly via CN IX, extreme posterior via CN X).
Motor innervation is via CN XII to hyoglossus (retracts and depresses tongue), genioglossus (protrudes tongue), and styloglossus (draws sides of tongue upward to create a trough for swallowing).
Motor innervation is via CN X to palatoglossus (elevates posterior tongue during swallowing).

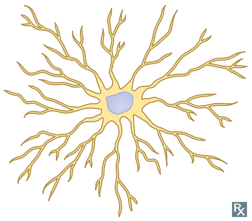
Taste—CN VII, IX, X (solitary nucleus).
Pain—CN V_3, IX, X.
Motor—CN X, XII.

▸ NEUROLOGY—ANATOMY AND PHYSIOLOGY

Neurons

Signal-transmitting cells of the nervous system. Permanent cells—do not divide in adulthood.
Signal-relaying cells with dendrites (receive input), cell bodies, and axons (send output). Cell bodies and dendrites can be seen on Nissl staining (stains RER). RER is not present in the axon.
Injury to axon → Wallerian degeneration—degeneration of axon distal to site of injury and axonal retraction proximally; allows for potential regeneration of axon (if in PNS). Macrophages remove debris and myelin.

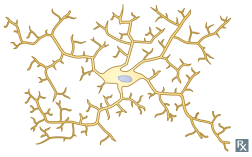
Astrocytes



Physical support, repair, extracellular K^+ buffer, removal of excess neurotransmitter, component of blood-brain barrier, glycogen fuel reserve buffer. Reactive gliosis in response to neural injury.

Derived from neuroectoderm. Astrocyte marker: GFAP.

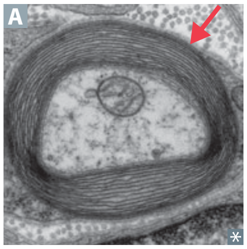
Microglia



Phagocytic scavenger cells of CNS (mesodermal, mononuclear origin). Activated in response to tissue damage. Not readily discernible by Nissl stain.

HIV-infected microglia fuse to form multinucleated giant cells in CNS.

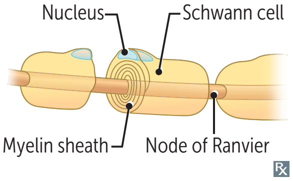
Myelin



↑ conduction velocity of signals transmitted down axons → saltatory conduction of action potential at the nodes of Ranvier, where there are high concentrations of Na^+ channels. Synthesis of myelin by oligodendrocytes in CNS and Schwann cells in PNS.

Wraps and insulates axons (arrow in A): ↑ space constant and ↑ conduction velocity.

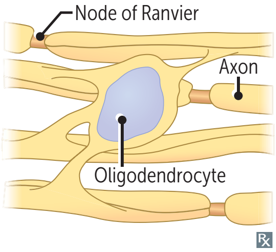
Schwann cells



Each Schwann cell myelinates only 1 PNS axon. Also promote axonal regeneration. Derived from neural crest.

May be injured in Guillain-Barré syndrome.

Oligodendrocytes



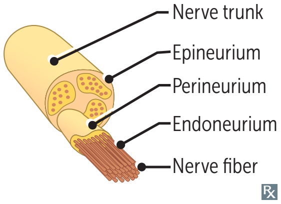
Myelinates axons of neurons in CNS. Each oligodendrocyte can myelinate many axons (~ 30). Predominant type of glial cell in white matter.

Derived from neuroectoderm. "Fried egg" appearance histologically. Injured in multiple sclerosis, progressive multifocal leukoencephalopathy (PML), leukodystrophies.

Sensory receptors

RECEPTOR TYPE	SENSORY NEURON FIBER TYPE	LOCATION	SENSES
Free nerve endings	C—slow, unmyelinated fibers Aδ—fast, myelinated fibers	All skin, epidermis, some viscera	Pain, temperature
Meissner corpuscles	Large, myelinated fibers; adapt quickly	Glabrous (hairless) skin	Dynamic, fine/light touch, position sense
Pacinian corpuscles	Large, myelinated fibers; adapt quickly	Deep skin layers, ligaments, joints	Vibration, pressure
Merkel discs	Large, myelinated fibers; adapt slowly	Finger tips, superficial skin	Pressure, deep static touch (eg, shapes, edges), position sense
Ruffini corpuscles	Dendritic endings with capsule; adapt slowly	Finger tips, joints	Pressure, slippage of objects along surface of skin, joint angle change

Peripheral nerve



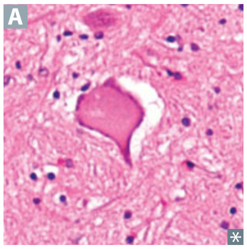
Endoneurium—invests single nerve fiber layers (inflammatory infiltrate in Guillain-Barré syndrome).

Perineurium (blood-nerve Permeability barrier)—surrounds a fascicle of nerve fibers. Must be rejoined in microsurgery for limb reattachment.

Epineurium—dense connective tissue that surrounds entire nerve (fascicles and blood vessels).

Endo = inner.
Peri = around.
Epi = outer.

Chromatolysis



Reaction of neuronal cell body to axonal injury. Changes reflect ↑ protein synthesis in effort to repair the damaged axon. Characterized by:

- Round cellular swelling A
- Displacement of the nucleus to the periphery
- Dispersion of Nissl substance throughout cytoplasm

Concurrent with Wallerian degeneration.

Neurotransmitter changes with disease

	LOCATION OF SYNTHESIS	ANXIETY	DEPRESSION	SCHIZOPHRENIA	ALZHEIMER DISEASE	HUNTINGTON DISEASE	PARKINSON DISEASE
Acetylcholine	Basal nucleus of Meynert				↓	↓	↑
Dopamine	Ventral tegmentum, SNc		↓	↑		↑	↓
GABA	Nucleus accumbens	↓				↓	
Norepinephrine	Locus ceruleus	↑	↓				
Serotonin	Raphe nucleus	↓	↓				↓

Meninges

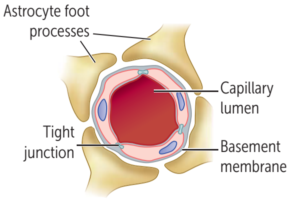
Three membranes that surround and protect the brain and spinal cord.

- Dura mater—thick outer layer closest to skull. Derived from mesoderm.
- Arachnoid mater—middle layer, contains web-like connections. Derived from neural crest.
- Pia mater—thin, fibrous inner layer that firmly adheres to brain and spinal cord. Derived from neural crest.

CSF flows in the subarachnoid space, located between arachnoid and pia mater.

Epidural space—a potential space between the dura mater and skull containing fat and blood vessels.

Blood-brain barrier



Prevents circulating blood substances (eg, bacteria, drugs) from reaching the CSF/CNS. Formed by 3 structures:

- Tight junctions between nonfenestrated capillary endothelial cells
- Basement membrane
- Astrocyte foot processes

Glucose and amino acids cross slowly by carrier-mediated transport mechanisms.

Nonpolar/lipid-soluble substances cross rapidly via diffusion.

A few specialized brain regions with fenestrated capillaries and no blood-brain barrier allow molecules in blood to affect brain function (eg, area postrema—vomiting after chemo; OVLT [organum vasculosum lamina terminalis]—osmotic sensing) or neurosecretory products to enter circulation (eg, neurohypophysis—ADH release).

Infarction and/or neoplasm destroys endothelial cell tight junctions → vasogenic edema.

Other notable barriers include:

- Blood-testis barrier
- Maternal-fetal blood barrier of placenta

Hypothalamus

Maintains homeostasis by regulating **T**hirst and water balance, controlling **A**denohyophysis (anterior pituitary) and **N**eurohypophysis (posterior pituitary) release of hormones produced in the hyopthalamus, and regulating **H**unger, **A**utonomic nervous system, **T**emperature, and **S**exual urges (**TAN HATS**).

Inputs (areas not protected by blood-brain barrier): OVLT (senses change in osmolarity), area postrema (found in medulla, responds to emetics).

Lateral area	Hunger. Destruction → anorexia, failure to thrive (infants). Stimulated by ghrelin, inhibited by leptin.	If you zap your **lateral** area, you shrink **lateral**ly.
Ventromedial area	Satiety. Destruction (eg, craniopharyngioma) → hyperphagia. Stimulated by leptin.	If you zap your **ventromedial** area, you grow **ventral**ly and **medial**ly.
Anterior hypothalamus	Cooling, parasympathetic.	**Anterior** nucleus = cool off (**cooling**, p**A**rasympathetic). **A/C** = **anterior cooling**.
Posterior hypothalamus	Heating, sympathetic.	Posterior nucleus = get fired up (heating, sympathetic). If you zap your **p**osterior hypothalamus, you become a **p**oikilotherm (cold-blooded, like a snake).
Suprachiasmatic nucleus	Circadian rhythm.	You need **sleep** to be **charismatic** (chiasmatic).
Supraoptic and paraventricular nuclei	Synthesize ADH and oxytocin	ADH and oxytocin are carried by neurophysins down axons to posterior pituitary, where these hormones are stored and released.

Sleep physiology

Sleep cycle is regulated by the circadian rhythm, which is driven by suprachiasmatic nucleus (SCN) of hypothalamus. Circadian rhythm controls nocturnal release of ACTH, prolactin, melatonin, norepinephrine: SCN → norepinephrine release → pineal gland → melatonin. SCN is regulated by environment (eg, light).

Two stages: rapid-eye movement (REM) and non-REM.

Alcohol, benzodiazepines, and barbiturates are associated with ↓ REM sleep and delta wave sleep; norepinephrine also ↓ REM sleep.

Oral desmopressin (ADH analog) is useful in treatment of bedwetting (sleep enuresis); preferred over imipramine because of the latter's adverse effects, although motivational therapy (eg, star chart) should still be first-line for bedwetting in children.

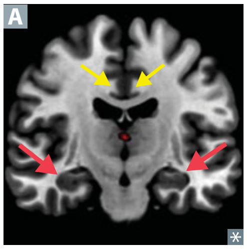
Benzodiazepines are useful for night terrors and sleepwalking by ↓ N3 and REM sleep.

SLEEP STAGE (% OF TOTAL SLEEP TIME IN YOUNG ADULTS)	DESCRIPTION	EEG WAVEFORM
Awake (eyes open)	Alert, active mental concentration	**B**eta (highest frequency, lowest amplitude)
Awake (eyes closed)		**A**lpha
Non-REM sleep		
Stage N1 (5%)	Light sleep	**T**heta
Stage N2 (45%)	Deeper sleep; when bruxism (teeth grinding) occurs	**S**leep spindles and K complexes
Stage N3 (25%)	Deepest non-REM sleep (slow-wave sleep); when sleepwalking, night terrors, and bedwetting occur	**D**elta (lowest frequency, highest amplitude)
REM sleep (25%)	Loss of motor tone, ↑ brain O_2 use, ↑ and variable pulse and blood pressure ↑ ACh; when dreaming, nightmares, and penile/clitoral tumescence occur; may serve memory processing function. Depression increases total REM sleep but decreases REM latency Extraocular movements due to activity of PPRF (paramedian pontine reticular formation/conjugate gaze center) Occurs every 90 minutes, and duration ↑ through the night	**B**eta At night, **BATS D**rink **B**lood

Thalamus Major relay for all ascending sensory information except olfaction.

NUCLEUS	INPUT	SENSES	DESTINATION	MNEMONIC
Ventral Postero-Lateral nucleus	Spinothalamic and dorsal columns/ medial lemniscus	Vibration, Pain, Pressure, Proprioception, Light touch, temperature	1° somatosensory cortex	
Ventral postero-Medial nucleus	Trigeminal and gustatory pathway	Face sensation, taste	1° somatosensory cortex	Makeup goes on the face
Lateral geniculate nucleus	CN II	Vision	Calcarine sulcus	Lateral = Light
Medial geniculate nucleus	Superior olive and inferior colliculus of tectum	Hearing	Auditory cortex of temporal lobe	Medial = Music
Ventral lateral nucleus	Basal ganglia, cerebellum	Motor	Motor cortex	

Limbic system



Collection of neural structures involved in emotion, long-term memory, olfaction, behavior modulation, ANS function.

Papez circuit consists of hippocampus (red arrows in A), mammillary bodies, anterior thalamic nuclei, cingulate gyrus (yellow arrows in A), entorhinal cortex. Responsible for Feeding, Fleeing, Fighting, Feeling, and Sex.

The famous 5 F's.

Dopaminergic pathways Commonly altered by drugs (eg, antipsychotics) and movement disorders (eg, Parkinson disease).

PATHWAY	SYMPTOMS OF ALTERED ACTIVITY	NOTES
Mesocortical	↓ activity → "negative" symptoms (eg, anergia, apathy, lack of spontaneity).	Antipsychotic drugs have limited effect.
Mesolimbic	↑ activity → "positive" symptoms (eg, delusions, hallucinations).	1° therapeutic target of antipsychotic drugs → ↓ positive symptoms (eg, in schizophrenia).
Nigrostriatal	↓ activity → extrapyramidal symptoms (eg, dystonia, akathisia, parkinsonism, tardive dyskinesia).	Major dopaminergic pathway in brain. Significantly affected by movement disorders and antipsychotic drugs.
Tuberoinfundibular	↓ activity → ↑ prolactin → ↓ libido, sexual dysfunction, galactorrhea, gynecomastia (in men).	

Cerebellum	Modulates movement; aids in coordination and balance. Input: ▪ Contralateral cortex via middle cerebellar peduncle. ▪ Ipsilateral proprioceptive information via inferior cerebellar peduncle from spinal cord. Output: ▪ The only output of cerebellar cortex = Purk**in**je cells (always **in**hibitory) → deep nuclei of cerebellum → contralateral cortex via superior cerebellar peduncle. ▪ Deep nuclei (lateral → medial)—**D**entate, **E**mboliform, **G**lobose, **F**astigial ("**D**on't **E**at **G**reasy **F**oods").	**L**ateral lesions—affect voluntary movement of extremities (**L**imbs); when injured, propensity to fall toward injured (ipsilateral) side. **M**edial lesions—involvement of **M**idline structures (vermal cortex, fastigial nuclei) and/or flocculonodular lobe → truncal ataxia (wide-based cerebellar gait), nystagmus, head tilting. Generally result in bilateral motor deficits affecting axial and proximal limb musculature.

Basal ganglia

Important in voluntary movements and making postural adjustments.

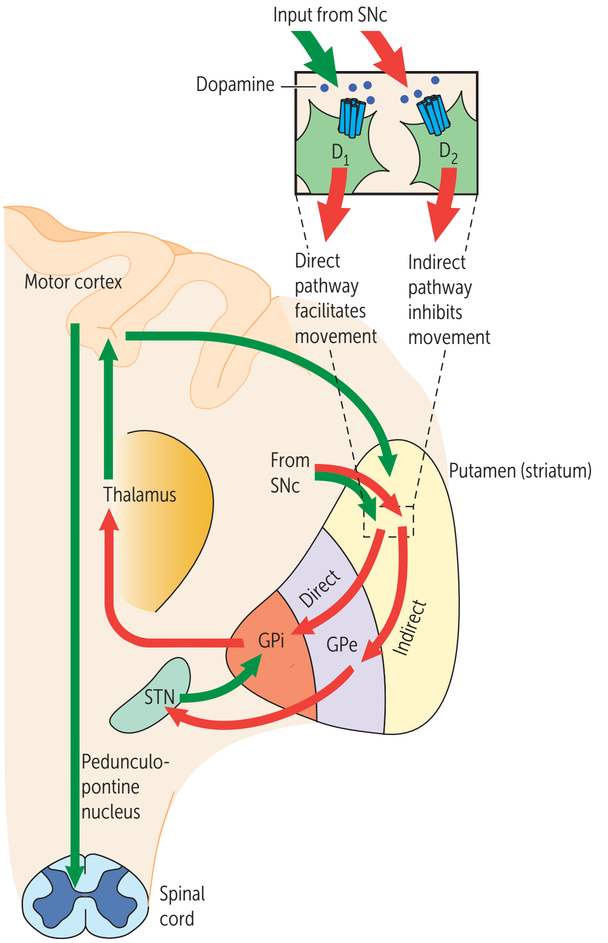
Receives cortical input, provides negative feedback to cortex to modulate movement.

Striatum = putamen (motor) + caudate (cognitive).

Lentiform = putamen + globus pallidus.

D_1-Receptor = **D1Rect** pathway.

Indirect = **In**hibitory.



Input from SNc
Dopamine
D_1
D_2
Direct pathway facilitates movement
Indirect pathway inhibits movement
Motor cortex
Thalamus
From SNc
Putamen (striatum)
Direct
Indirect
GPi
GPe
STN
Pedunculo-pontine nucleus
Spinal cord

🟩 Stimulatory

🟥 Inhibitory

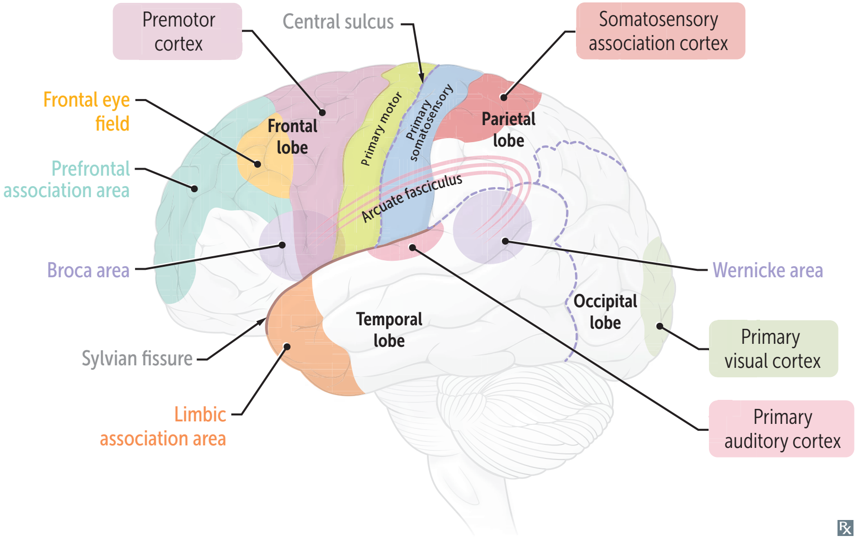
SNc	Substantia nigra pars compacta
GPe	Globus pallidus externus
GPi	Globus pallidus internus
STN	Subthalamic nucleus
D_1	Dopamine D_1 receptor
D_2	Dopamine D_2 receptor

Excitatory pathway—cortical inputs stimulate the striatum, stimulating the release of GABA, which inhibits GABA release from the GPi, disinhibiting the thalamus via the GPi (↑ motion).

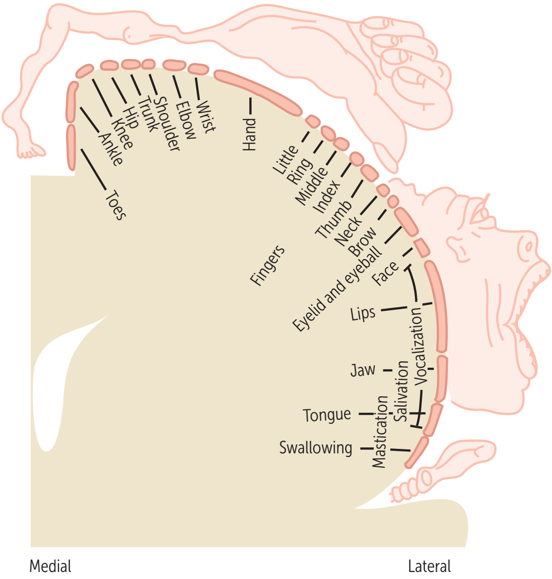
Inhibitory pathway—cortical inputs stimulate the striatum, releasing GABA that disinhibits STN via GPe inhibition, and STN stimulates GPi to inhibit the thalamus (↓ motion).

Dopamine binds to D_1, stimulating the excitatory pathway, and to D_2, inhibiting the inhibitory pathway → ↑ motion.

Cerebral cortex regions


Premotor cortex
Central sulcus
Somatosensory association cortex
Frontal eye field
Prefrontal association area
Frontal lobe
Primary motor
Primary somatosensory
Parietal lobe
Arcuate fasciculus
Broca area
Wernicke area
Occipital lobe
Temporal lobe
Primary visual cortex
Sylvian fissure
Limbic association area
Primary auditory cortex

Homunculus


Toes
Ankle
Knee
Hip
Trunk
Shoulder
Elbow
Wrist
Hand
Little
Ring
Middle
Index
Thumb
Neck
Brow
Eyelid and eyeball
Face
Fingers
Lips
Jaw
Tongue
Swallowing
Mastication
Salivation
Vocalization
Medial
Lateral

Topographic representation of motor (shown) and sensory areas in the cerebral cortex. Distorted appearance is due to certain body regions being more richly innervated and thus having ↑ cortical representation.

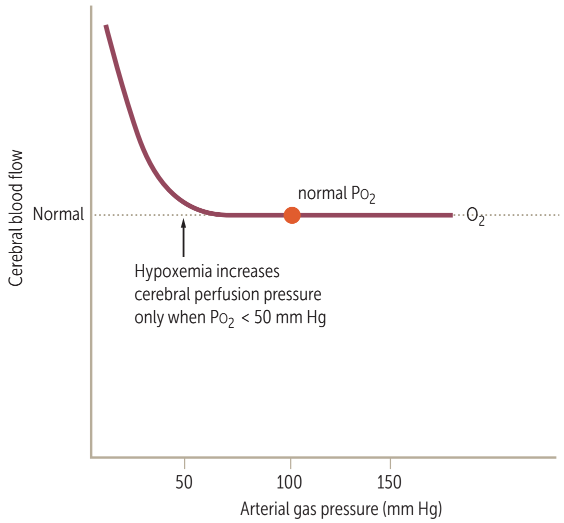
Cerebral perfusion

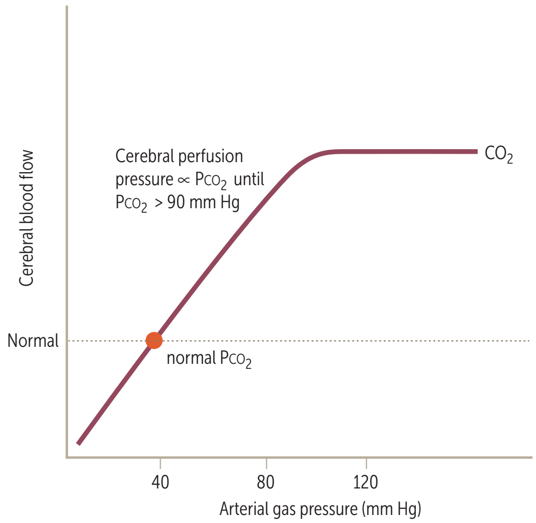
Brain perfusion relies on tight autoregulation. Cerebral perfusion is primarily driven by Pco_2 (Po_2 also modulates perfusion in severe hypoxia).

Cerebral perfusion relies on a pressure gradient between mean arterial pressure (MAP) and ICP. ↓ blood pressure or ↑ ICP → ↓ cerebral perfusion pressure (CPP).

Therapeutic hyperventilation → ↓ Pco_2 → vasoconstriction → ↓ cerebral blood flow → ↓ intracranial pressure (ICP). May be used to treat acute cerebral edema (eg, 2° to stroke) unresponsive to other interventions.

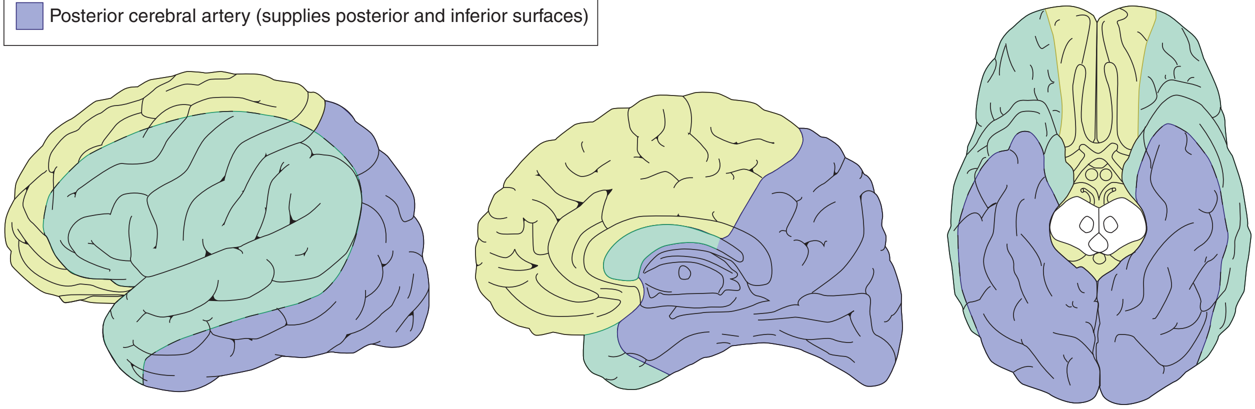
CPP = MAP – ICP. If CPP = 0, there is no cerebral perfusion → brain death.





Cerebral arteries—cortical distribution

🟨 Anterior cerebral artery (supplies anteromedial surface)
🟩 Middle cerebral artery (supplies lateral surface)
🟦 Posterior cerebral artery (supplies posterior and inferior surfaces)

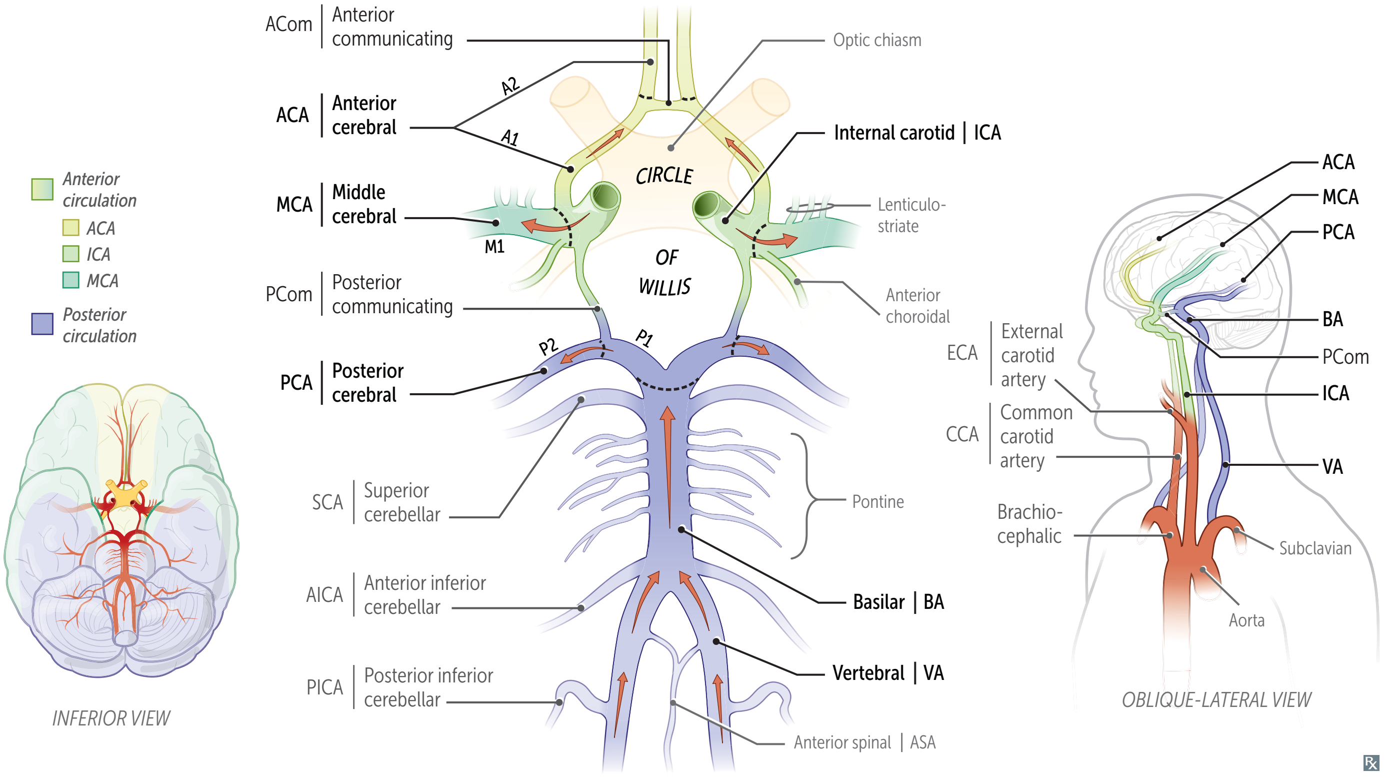


Watershed zones

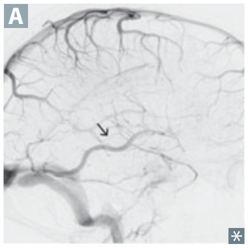
Between anterior cerebral/middle cerebral, posterior cerebral/middle cerebral arteries. Damage by severe hypotension → upper leg/upper arm weakness, defects in higher-order visual processing.

Circle of Willis

System of anastomoses between anterior and posterior blood supplies to brain.

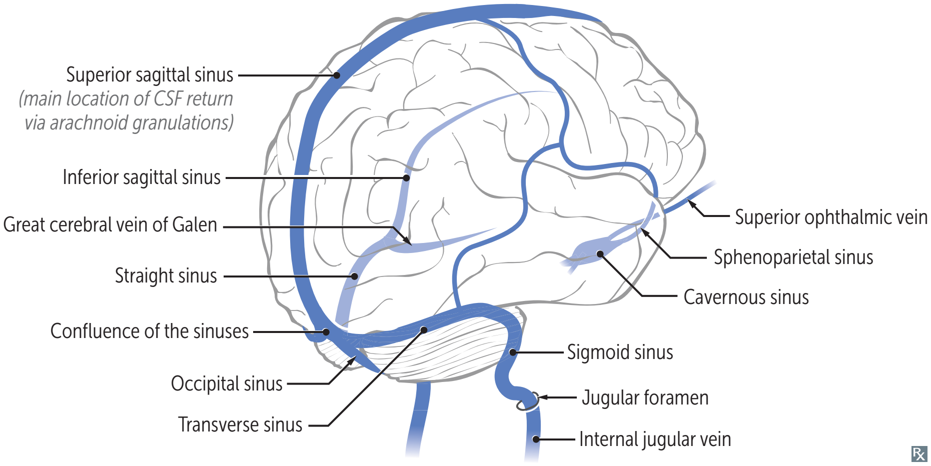

ACom | Anterior communicating
ACA | Anterior cerebral
A2
A1
MCA | Middle cerebral
M1
PCom | Posterior communicating
PCA | Posterior cerebral
P2
P1
SCA | Superior cerebellar
AICA | Anterior inferior cerebellar
PICA | Posterior inferior cerebellar
Optic chiasm
Internal carotid | ICA
CIRCLE OF WILLIS
Lenticulo-striate
Anterior choroidal
Pontine
Basilar | BA
Vertebral | VA
Anterior spinal | ASA
Anterior circulation
ACA
ICA
MCA
Posterior circulation
INFERIOR VIEW
ACA
MCA
PCA
BA
PCom
ICA
VA
ECA | External carotid artery
CCA | Common carotid artery
Brachio-cephalic
Subclavian
Aorta
OBLIQUE-LATERAL VIEW

Dural venous sinuses



Large venous channels A that run through the dura. Drain blood from cerebral veins (arrow) and receive CSF from arachnoid granulations. Empty into internal jugular vein.

Venous sinus thrombosis—presents with signs/symptoms of ↑ ICP (eg, headache, seizures, focal neurologic deficits). May lead to venous hemorrhage. Associated with hypercoagulable states (eg, pregnancy, OCP use, factor V Leiden).


Superior sagittal sinus (main location of CSF return via arachnoid granulations)
Inferior sagittal sinus
Great cerebral vein of Galen
Straight sinus
Confluence of the sinuses
Occipital sinus
Transverse sinus
Superior ophthalmic vein
Sphenoparietal sinus
Cavernous sinus
Sigmoid sinus
Jugular foramen
Internal jugular vein

Ventricular system

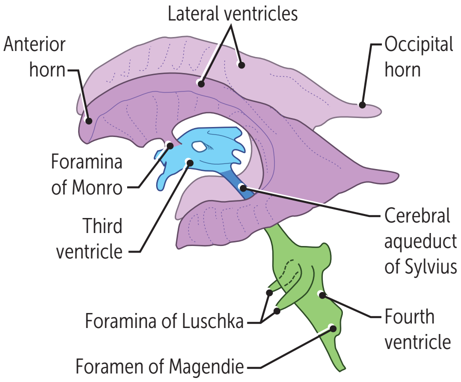
Lateral ventricles → 3rd ventricle via right and left interventricular foramina of Monro.

3rd ventricle → 4th ventricle via cerebral aqueduct of Sylvius.

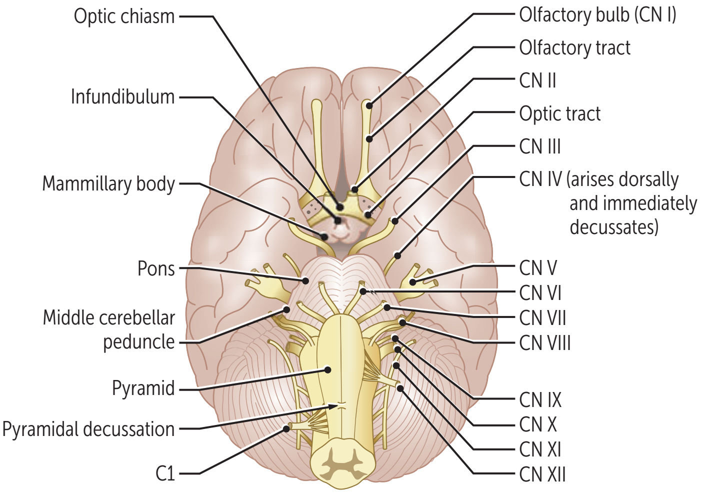
4th ventricle → subarachnoid space via:

- Foramina of **L**uschka = **L**ateral.
- Foramen of **M**agendie = **M**edial.

CSF is made by ependymal cells of choroid plexus; it is reabsorbed by arachnoid granulations and then drains into dural venous sinuses.


Lateral ventricles
Anterior horn
Occipital horn
Foramina of Monro
Third ventricle
Cerebral aqueduct of Sylvius
Foramina of Luschka
Fourth ventricle
Foramen of Magendie

Brain stem—ventral view

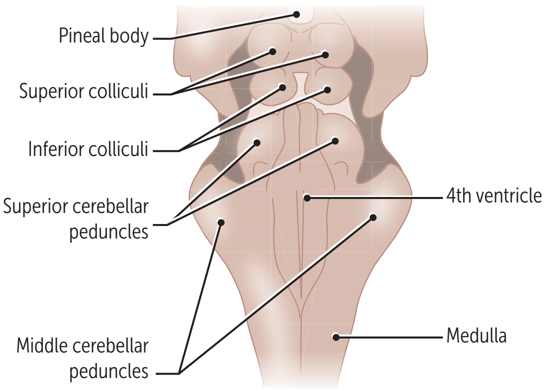

Optic chiasm
Infundibulum
Mammillary body
Pons
Middle cerebellar peduncle
Pyramid
Pyramidal decussation
C1
Olfactory bulb (CN I)
Olfactory tract
CN II
Optic tract
CN III
CN IV (arises dorsally and immediately decussates)
CN V
CN VI
CN VII
CN VIII
CN IX
CN X
CN XI
CN XII

4 CN are above pons (I, II, III, IV).

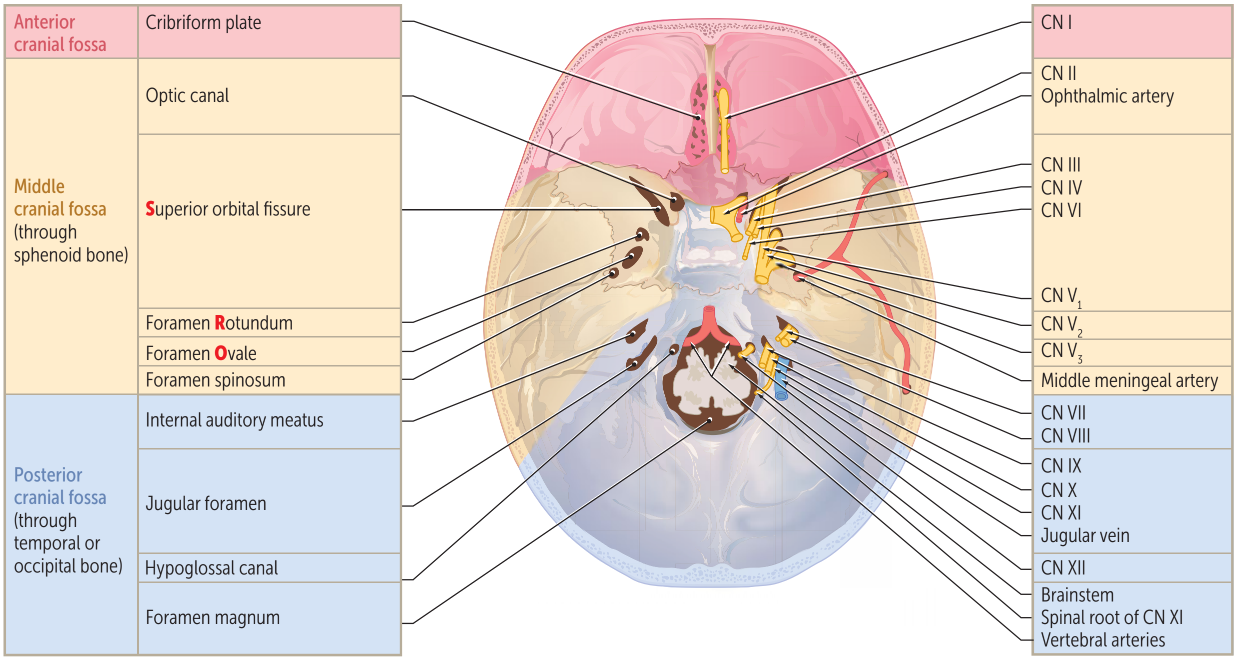
4 CN are in pons (V, VI, VII, VIII).

4 CN are in medulla (IX, X, XI, XII).

4 CN nuclei are medial (III, IV, VI, XII). “Factors of 12, except 1 and 2.”

Brain stem—dorsal view (cerebellum removed)	Pineal gland—melatonin secretion, circadian rhythms. Superior colliculi—conjugate vertical gaze center. Inferior colliculi—auditory.	Your eyes are **above** your ears, and the superior colliculus (visual) is **above** the inferior colliculus (auditory).  Pineal body Superior colliculi Inferior colliculi Superior cerebellar peduncles Middle cerebellar peduncles 4th ventricle Medulla
Cranial nerve nuclei	Located in tegmentum portion of brain stem (between dorsal and ventral portions): - Midbrain—nuclei of CN III, IV - Pons—nuclei of CN V, VI, VII, VIII - Medulla—nuclei of CN IX, X, XII - Spinal cord—nucleus of CN XI	**L**ateral nuclei = sensory (a**L**ar plate). —Sulcus limitans— **M**edial nuclei = **M**otor (basal plate).

Cranial nerve and vessel pathways


Anterior cranial fossa
Cribriform plate
Middle cranial fossa (through sphenoid bone)
Optic canal
Superior orbital fissure
Foramen Rotundum
Foramen Ovale
Foramen spinosum
Posterior cranial fossa (through temporal or occipital bone)
Internal auditory meatus
Jugular foramen
Hypoglossal canal
Foramen magnum
CN I
CN II
Ophthalmic artery
CN III
CN IV
CN VI
CN V_1
CN V_2
CN V_3
Middle meningeal artery
CN VII
CN VIII
CN IX
CN X
CN XI
Jugular vein
CN XII
Brainstem
Spinal root of CN XI
Vertebral arteries

Divisions of CNV exit owing to Standing Room Only

Cranial nerves

NERVE	CN	FUNCTION	TYPE	MNEMONIC
Olfactory	I	Smell (only CN without thalamic relay to cortex)	Sensory	Some
Optic	II	Sight	Sensory	Say
Oculomotor	III	Eye movement (SR, IR, MR, IO), pupillary constriction (sphincter pupillae: Edinger-Westphal nucleus, muscarinic receptors), accommodation, eyelid opening (levator palpebrae)	Motor	Marry
Trochlear	IV	Eye movement (SO)	Motor	Money
Trigeminal	V	Mastication, facial sensation (ophthalmic, maxillary, mandibular divisions), somatosensation from anterior $^{2}/_{3}$ of tongue	Both	But
Abducens	VI	Eye movement (LR)	Motor	My
Facial	VII	Facial movement, taste from anterior $^{2}/_{3}$ of tongue, lacrimation, salivation (submandibular and sublingual glands), eyelid closing (orbicularis oculi), auditory volume modulation (stapedius)	Both	Brother
Vestibulocochlear	VIII	Hearing, balance	Sensory	Says
Glossopharyngeal	IX	Taste and sensation from posterior $^{1}/_{3}$ of tongue, swallowing, salivation (parotid gland), monitoring carotid body and sinus chemo- and baroreceptors, and elevation of pharynx/larynx (stylopharyngeus)	Both	Big
Vagus	X	Taste from supraglottic region, swallowing, soft palate elevation, midline uvula, talking, cough reflex, parasympathetics to thoracoabdominal viscera, monitoring aortic arch chemo- and baroreceptors	Both	Brains
Accessory	XI	Head turning, shoulder shrugging (SCM, trapezius)	Motor	Matter
Hypoglossal	XII	Tongue movement	Motor	Most

Vagal nuclei

NUCLEUS	FUNCTION	CRANIAL NERVES
Nucleus Solitarius	Visceral Sensory information (eg, taste, baroreceptors, gut distention)	VII, IX, X
Nucleus aMbiguus	Motor innervation of pharynx, larynx, upper esophagus (eg, swallowing, palate elevation)	IX, X, XI (cranial portion)
Dorsal motor nucleus	Sends autonomic (parasympathetic) fibers to heart, lungs, upper GI	X

Cranial nerve reflexes

REFLEX	AFFERENT	EFFERENT
Corneal	V_1 ophthalmic (nasociliary branch)	VII (temporal branch: orbicularis oculi)
Lacrimation	V_1 (loss of reflex does not preclude emotional tears)	VII
Jaw jerk	V_3 (sensory—muscle spindle from masseter)	V_3 (motor—masseter)
Pupillary	II	III
Gag	IX	X

Mastication muscles	3 muscles close jaw: Masseter, teMporalis, Medial pterygoid. 1 opens: Lateral pterygoid. All are innervated by trigeminal nerve (V_3).	M's Munch. Lateral Lowers (when speaking of pterygoids with respect to jaw motion). "It takes more muscle to keep your mouth shut."

Spinal nerves

There are 31 pairs of spinal nerves in total: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.

Nerves C1–C7 exit above the corresponding vertebra. C8 spinal nerve exits below C7 and above T1. All other nerves exit below (eg, C3 exits above the 3rd cervical vertebra; L2 exits below the 2nd lumbar vertebra).

Vertebral disc herniation—nucleus pulposus (soft central disc) herniates through annulus fibrosus (outer ring); usually occurs posterolaterally at L4–L5 or L5–S1. Nerve usually affected is below the level of herniation (eg, L3–L4 disc spares L3 nerve and involves L4 nerve). Compression of S1 nerve root → absent ankle reflex.

Spinal cord—lower extent

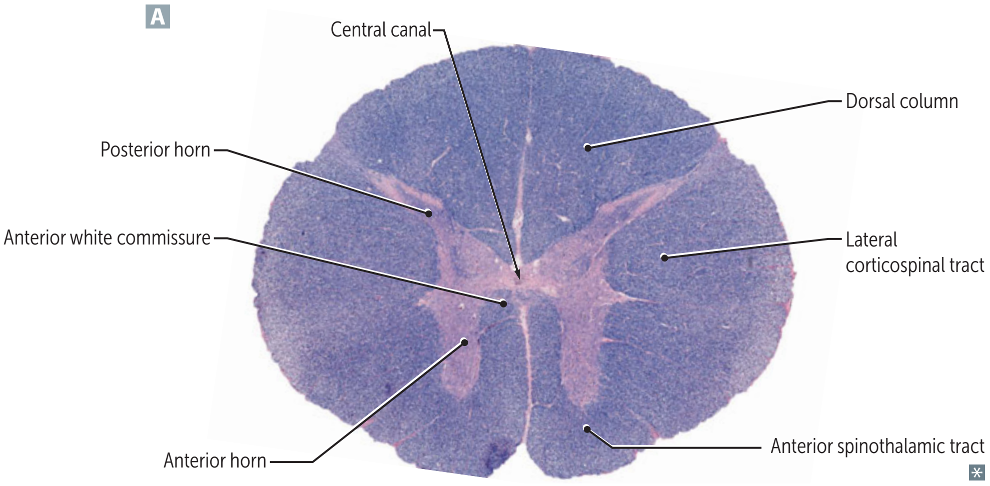
In adults, spinal cord ends at lower border of L1–L2 vertebrae. Subarachnoid space (which contains the CSF) extends to lower border of S2 vertebra. Lumbar puncture is usually performed between L3–L4 or L4–L5 (level of cauda equina).

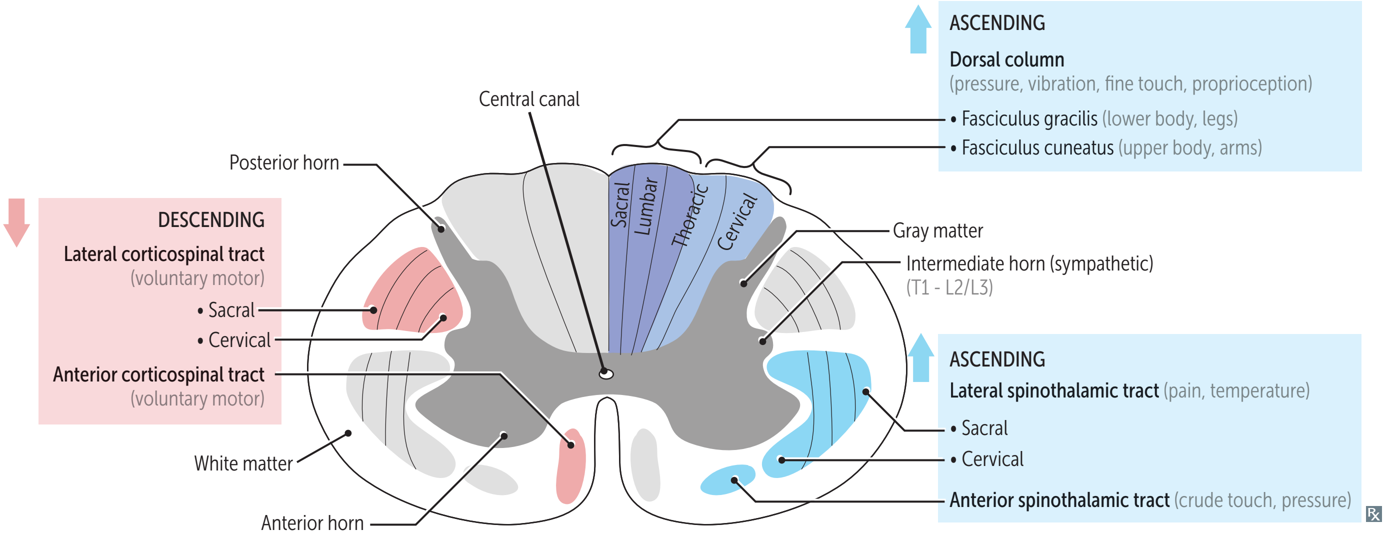
Goal of lumbar puncture is to obtain sample of CSF without damaging spinal cord. To **keep** the cord **alive**, keep the spinal needle between **L3** and **L5**.

Spinal cord and associated tracts

Legs (**L**umbosacral) are **L**ateral in **L**ateral corticospinal, spinothalamic tracts A.

Dorsal columns are organized as you are, with hands at sides. "Arms outside, legs inside."


A
Central canal
Dorsal column
Posterior horn
Anterior white commissure
Lateral corticospinal tract
Anterior horn
Anterior spinothalamic tract

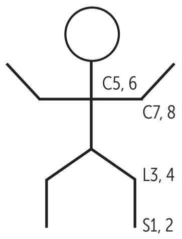

ASCENDING
Dorsal column
(pressure, vibration, fine touch, proprioception)
• Fasciculus gracilis (lower body, legs)
• Fasciculus cuneatus (upper body, arms)
Central canal
Posterior horn
Sacral
Lumbar
Thoracic
Cervical
Gray matter
Intermediate horn (sympathetic)
(T1 - L2/L3)
DESCENDING
Lateral corticospinal tract
(voluntary motor)
• Sacral
• Cervical
Anterior corticospinal tract
(voluntary motor)
ASCENDING
Lateral spinothalamic tract (pain, temperature)
• Sacral
• Cervical
Anterior spinothalamic tract (crude touch, pressure)
White matter
Anterior horn

Spinal tract anatomy and functions

Ascending tracts synapse and then cross.

TRACT	FUNCTION	1ST-ORDER NEURON	SYNAPSE 1	2ND-ORDER NEURON	SYNAPSE 2 + PROJECTIONS
Ascending tracts					
Dorsal column	Pressure, vibration, fine touch, proprioception	Sensory nerve ending → bypass pseudounipolar cell body in dorsal root ganglion → enter spinal cord → ascend ipsilaterally in dorsal columns	Nucleus gracilis, nucleus cuneatus (ipsilateral medulla)	Decussates in medulla → ascends contralaterally in medial lemniscus	VPL (thalamus) → sensory cortex
Spinothalamic tract	Lateral: pain, temperature Anterior: crude touch, pressure	Sensory nerve ending (Aδ and C fibers) → bypass pseudounipolar cell body in dorsal root ganglion → enter spinal cord	Ipsilateral gray matter (spinal cord)	Decussates at anterior white commissure → ascends contralaterally	
Descending tract					
Lateral corticospinal tract	Voluntary movement of contralateral limbs	UMN: cell body in 1° motor cortex → descends ipsilaterally (through internal capsule), most fibers decussate at caudal medulla (pyramidal decussation) → descends contralaterally	Cell body of anterior horn (spinal cord)	LMN: leaves spinal cord	NMJ → muscle fibers

Clinical reflexes



Reflexes count up in order (main nerve root bolded):

Achilles reflex = **S1**, S2 (“buckle my shoe”)
Patellar reflex = L3, **L4** (“kick the door”)
Biceps and brachioradialis reflexes = **C5**, C6 (“pick up sticks”)
Triceps reflex = **C7**, C8 (“lay them straight”)

Additional reflexes:

Cremasteric reflex = L1, L2 (“testicles move”)
Anal wink reflex = S3, S4 (“winks galore”)

Primitive reflexes

CNS reflexes that are present in a healthy infant, but are absent in a neurologically intact adult. Normally disappear within 1st year of life. These “primitive” reflexes are inhibited by a mature/developing frontal lobe. They may reemerge in adults following frontal lobe lesions → loss of inhibition of these reflexes.

Moro reflex	“Hang on for life” reflex—abduct/extend arms when startled, and then draw together
Rooting reflex	Movement of head toward one side if cheek or mouth is stroked (nipple seeking)
Sucking reflex	Sucking response when roof of mouth is touched
Palmar reflex	Curling of fingers if palm is stroked
Plantar reflex	Dorsiflexion of large toe and fanning of other toes with plantar stimulation Babinski sign—presence of this reflex in an adult, which may signify a UMN lesion
Galant reflex	Stroking along one side of the spine while newborn is in ventral suspension (face down) causes lateral flexion of lower body toward stimulated side

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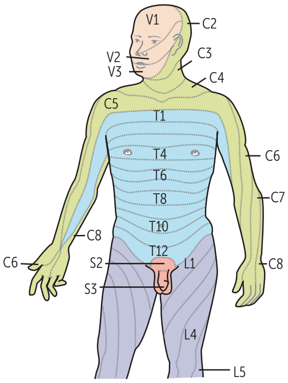
Landmark dermatomes



C2—posterior half of the skull.
C3—high turtleneck shirt.
C4—low-collar shirt.
C6—includes thumbs.
T4—at the nipple.
T7—at the xiphoid process.
T10—at the umbilicus (important for early appendicitis pain referral).
L1—at the inguinal ligament.
L4—includes the kneecaps.
S2, S3, S4—erection and sensation of penile and anal zones.

Diaphragm and gallbladder pain referred to the right shoulder via phrenic nerve (C3–C5).

Thumbs up sign on left hand looks like a six for C6.
T4 at the teat pore.

T10 at the belly butten.

L1 is IL (Inguinal Ligament).
Down on ALL 4’s (L4).
“S2, 3, 4 keep the penis off the floor.”

▸ NEUROLOGY—NEUROPATHOLOGY

Common brain lesions

AREA OF LESION	CONSEQUENCE	EXAMPLES
Frontal lobe	Disinhibition and deficits in concentration, orientation, judgment; may have reemergence of primitive reflexes.	
Frontal eye fields	Eyes look toward lesion.	
Paramedian pontine reticular formation	Eyes look away from side of lesion.	
Medial longitudinal fasciculus	Internuclear ophthalmoplegia (impaired adduction of ipsilateral eye; nystagmus of contralateral eye with abduction).	Multiple sclerosis.
Dominant parietal cortex	Agraphia, acalculia, finger agnosia, left-right disorientation.	Gerstmann syndrome.
Nondominant parietal cortex	Agnosia of the contralateral side of the world.	Hemispatial neglect syndrome.
Hippocampus (bilateral)	Anterograde amnesia—inability to make new memories.	
Basal ganglia	May result in tremor at rest, chorea, athetosis.	Parkinson disease, Huntington disease.
Subthalamic nucleus	Contralateral hemiballismus.	
Mammillary bodies (bilateral)	Wernicke-Korsakoff syndrome—**C**onfusion, **A**taxia, **N**ystagmus, **O**phthalmoplegia, memory loss (anterograde and retrograde amnesia), confabulation, personality changes.	Wernicke problems come in a **CAN O'** beer.
Amygdala (bilateral)	Klüver-Bucy syndrome—disinhibited behavior (eg, hyperphagia, hypersexuality, hyperorality).	HSV-1 encephalitis.
Superior colliculus	Parinaud syndrome—paralysis of conjugate vertical gaze (rostral interstitial nucleus also involved).	Stroke, hydrocephalus, pinealoma.
Reticular activating system (midbrain)	Reduced levels of arousal and wakefulness (eg, coma).	
Cerebellar hemisphere	Intention tremor, limb ataxia, loss of balance; damage to cerebellum → ipsilateral deficits; fall toward side of lesion.	Cerebellar hemispheres are **laterall**y located—affect **lateral** limbs.
Cerebellar vermis	Truncal ataxia, dysarthria.	Vermis is **centrall**y located—affects **central** body. Degeneration associated with chronic alcohol use.

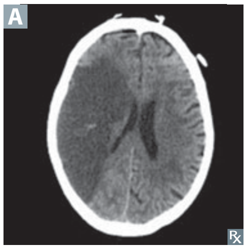
Ischemic brain disease/stroke

Irreversible damage begins after 5 minutes of hypoxia. Most vulnerable: hippocampus, neocortex, cerebellum, watershed areas. Irreversible neuronal injury. **Hippo**campus is most **vulnerable** to ischemic hypoxia ("**vulnerable hippo**s").

Stroke imaging: noncontrast CT to exclude hemorrhage (before tPA can be given). CT detects ischemic changes in 6–24 hr. Diffusion-weighted MRI can detect ischemia within 3–30 min.

TIME SINCE ISCHEMIC EVENT	12–24 HOURS	24–72 HOURS	3–5 DAYS	1–2 WEEKS	> 2 WEEKS
Histologic features	Red neurons (eosinophilic cytoplasm with pyknotic nuclei)	Necrosis + neutrophils	Macrophages (microglia)	Reactive gliosis + vascular proliferation	Glial scar

Ischemic stroke



Acute blockage of vessels → disruption of blood flow and subsequent ischemia → liquefactive necrosis.

3 types:

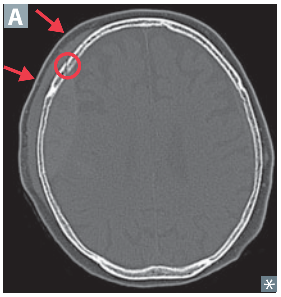
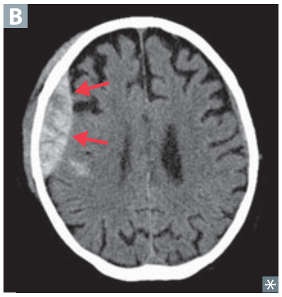
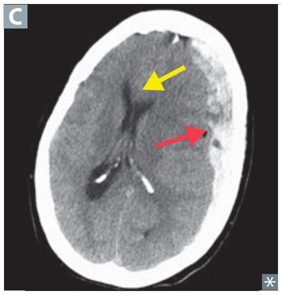
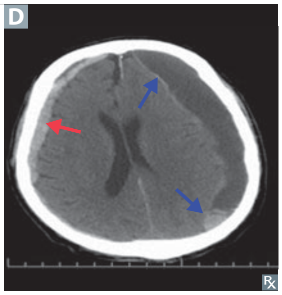
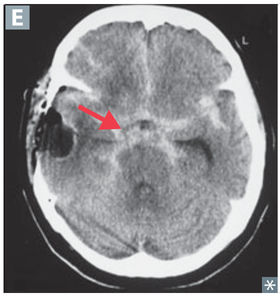
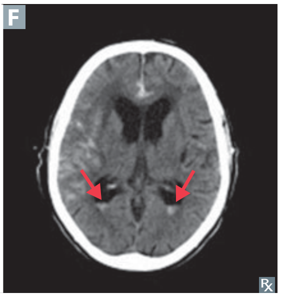
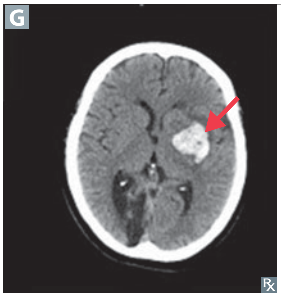
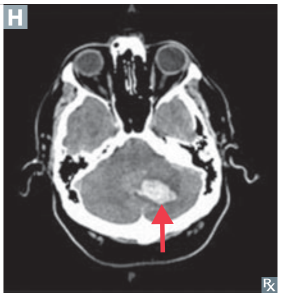
- Thrombotic—due to a clot forming directly at site of infarction (commonly the MCA A), usually over an atherosclerotic plaque.
- Embolic—embolus from another part of the body obstructs vessel. Can affect multiple vascular territories. Examples: atrial fibrillation; DVT with patent foramen ovale.
- Hypoxic—due to hypoperfusion or hypoxemia. Common during cardiovascular surgeries, tends to affect watershed areas.

Treatment: tPA (if within 3–4.5 hr of onset and no hemorrhage/risk of hemorrhage). Reduce risk with medical therapy (eg, aspirin, clopidogrel); optimum control of blood pressure, blood sugars, lipids; and treat conditions that ↑ risk (eg, atrial fibrillation).

Transient ischemic attack

Brief, reversible episode of focal neurologic dysfunction without acute infarction (⊖ MRI), with the majority resolving in < 15 minutes; deficits due to focal ischemia.

Intracranial hemorrhage

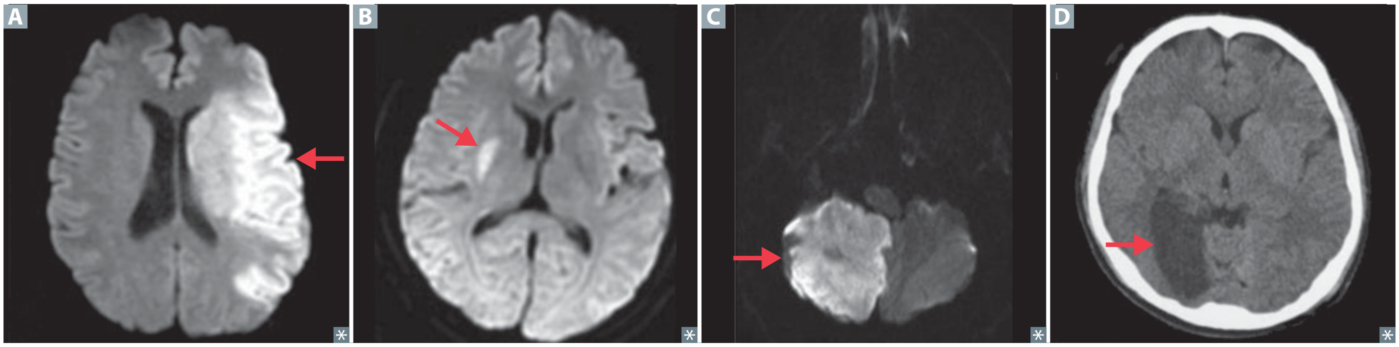
Epidural hematoma	Rupture of middle meningeal artery (branch of maxillary artery), often 2° to skull fracture A involving the pterion (thinnest area of the lateral skull). Lucid interval. Rapid expansion under systemic arterial pressure → transtentorial herniation, CN III palsy. CT shows biconvex (lentiform), hyperdense blood collection B **not crossing suture lines.**		
Subdural hematoma	Rupture of bridging veins. Can be acute (traumatic, high-energy impact → hyperdense on CT) or chronic (associated with mild trauma, cerebral atrophy, elderly, alcoholism → hypodense on CT). Also seen in shaken babies. Predisposing factors: brain atrophy, trauma. Crescent-shaped hemorrhage (red arrows in C and D) that crosses suture lines. Can cause midline shift (yellow arrow in C), findings of "acute on chronic" hemorrhage (blue arrows in D).		
Subarachnoid hemorrhage	Bleeding E F due to trauma, or rupture of an aneurysm (such as a saccular aneurysm E) or arteriovenous malformation. Rapid time course. Patients complain of "worst headache of my life." Bloody or yellow (xanthochromic) spinal tap. 4–10 days after hemorrhage, vasospasm (narrowing of blood vessels) can occur due to blood breakdown or rebleed → ischemic infarct; nimodipine used to prevent/reduce vasospasm. ↑ risk of developing communicating and/or obstructive hydrocephalus.		
Intraparenchymal hemorrhage	Most commonly caused by systemic hypertension. Also seen with amyloid angiopathy (recurrent lobar hemorrhagic stroke in elderly), vasculitis, neoplasm. May be 2° to reperfusion injury in ischemic stroke. Typically occurs in basal ganglia G and internal capsule (Charcot-Bouchard microaneurysm of lenticulostriate vessels), but can also occur in cerebral hemispheres, brainstem, and cerebellum H.		

Effects of strokes

ARTERY	AREA OF LESION	SYMPTOMS	NOTES
Anterior circulation			
Middle cerebral artery	Motor and sensory cortices A—upper limb and face.	Contralateral paralysis and sensory loss—face and upper limb.	Wernicke aphasia is associated with right superior quadrant visual field defect due to temporal lobe involvement.
	Temporal lobe (Wernicke area); frontal lobe (Broca area).	Aphasia if in dominant (usually left) hemisphere. Hemineglect if lesion affects nondominant (usually right) side.	
Anterior cerebral artery	Motor and sensory cortices—lower limb.	Contralateral paralysis and sensory loss—lower limb.	
Lenticulo-striate artery	Striatum, internal capsule.	Contralateral paralysis and/or sensory loss—face and body. Absence of cortical signs (eg, neglect, aphasia, visual field loss).	Common location of lacunar infarcts B, due to hyaline arteriosclerosis 2° to unmanaged hypertension.
Posterior circulation			
Anterior spinal artery	Lateral corticospinal tract.	Contralateral paralysis—upper and lower limbs.	Medial medullary syndrome—caused by infarct of paramedian branches of ASA and/or vertebral arteries.
	Medial lemniscus.	↓ contralateral proprioception.	
	Caudal medulla—hypoglossal nerve.	Ipsilateral hypoglossal dysfunction (tongue deviates ipsilaterally).	
Posterior inferior cerebellar artery	Lateral medulla:		Lateral medullary (Wallenberg) syndrome. Nucleus ambiguus effects are specific to PICA lesions C. "Don't **pick a** (**PICA**) **horse** (hoarseness) that **can't eat** (dysphagia)." Also supplies inferior cerebellar peduncle (part of cerebellum).
	Nucleus ambiguus (CN IX, X, XI)	**Dysphagia, hoarseness, ↓ gag reflex**	
	Vestibular nuclei	Vomiting, vertigo, nystagmus	
	Lateral spinothalamic tract, spinal trigeminal nucleus	↓ pain and temperature sensation from contralateral body, ipsilateral face	
	Sympathetic fibers	Ipsilateral Horner syndrome	
	Inferior cerebellar peduncle	Ataxia, dysmetria	
Anterior inferior cerebellar artery	Lateral pons		Lateral pontine syndrome. Facial nucleus effects are specific to AICA lesions. "**Facial droop** means AICA's **pooped**." Also supplies middle and inferior cerebellar peduncles (part of cerebellum).
	Facial nucleus	**Paralysis of face**, ↓ lacrimation, ↓ salivation, ↓ taste from anterior ⅔ of tongue	
	Vestibular nuclei	Vomiting, vertigo, nystagmus	
	Spinothalamic tract, spinal trigeminal nucleus	↓ pain and temperature sensation from contralateral body, ipsilateral face	
	Sympathetic fibers	Ipsilateral Horner syndrome	
	Middle and inferior cerebellar peduncles	Ataxia, dysmetria	

Effects of strokes *(continued)*

ARTERY	AREA OF LESION	SYMPTOMS	NOTES
Basilar artery	Pons, medulla, lower midbrain	RAS spared, therefore preserved consciousness	"Locked-in syndrome."
	Corticospinal and corticobulbar tracts	Quadriplegia; loss of voluntary facial, mouth, and tongue movements	
	Ocular cranial nerve nuclei, paramedian pontine reticular formation	Loss of horizontal, but not vertical, eye movements	
Posterior cerebral artery	Occipital lobe D.	Contralateral hemianopia with macular sparing.	



Central post-stroke pain syndrome

Neuropathic pain due to thalamic lesions. Initial paresthesias followed in weeks to months by allodynia (ordinarily painless stimuli cause pain) and dysesthesia. Occurs in 10% of stroke patients.

Aphasia

Aphasia—higher-order language deficit (inability to understand/speak/read/write).
Dysarthria—motor inability to speak (movement deficit).

TYPE	SPEECH FLUENCY	COMPREHENSION	COMMENTS
Repetition impaired			
Broca (expressive)	Nonfluent	Intact	Broca = Broken Boca (*boca* = mouth in Spanish). Broca area in inferior frontal gyrus of frontal lobe. Patient appears frustrated, insight intact.
Wernicke (receptive)	Fluent	Impaired	Wernicke is Wordy but makes no sense. Patients do not have insight. Wernicke area in superior temporal gyrus of temporal lobe.
Conduction	Fluent	Intact	Can be caused by damage to arCuate fasciculus.
Global	Nonfluent	Impaired	Arcuate fasciculus; Broca and Wernicke areas affected (all areas).
Repetition intact			
Transcortical motor	Nonfluent	Intact	Affects frontal lobe around Broca area, but Broca area is spared.
Transcortical sensory	Fluent	Impaired	Affects temporal lobe around Wernicke area, but Wernicke area is spared.
Transcortical, mixed	Nonfluent	Impaired	Broca and Wernicke areas and arcuate fasciculus remain intact; surrounding watershed areas affected.

Aneurysms

Abnormal dilation of an artery due to weakening of vessel wall.

Saccular (berry) aneurysm

Occurs at bifurcations in the circle of Willis. Most common site is junction of ACom and ACA. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, smoking, race (↑ risk in African-Americans).

Usually clinically silent until rupture (most common complication) → subarachnoid hemorrhage (“worst headache of my life” or “thunderclap headache”) → focal neurologic deficits. Can also cause symptoms via direct compression on surrounding structures by growing aneurysm.

- ACom—compression → bitemporal hemianopia (compression of optic chiasm); visual acuity deficits; rupture → ischemia in ACA distribution → contralateral lower extremity hemiparesis, sensory deficits.
- MCA—rupture → ischemia in MCA distribution → contralateral upper extremity and facial hemiparesis, sensory deficits.
- PCom—compression → ipsilateral CN III palsy → mydriasis (“blown pupil”); may also see ptosis, “down and out” eye.

Charcot-Bouchard microaneurysm

Common, associated with chronic hypertension; affects small vessels (eg, lenticulostriate arteries in basal ganglia, thalamus). Not visible on angiography.

Seizures	Characterized by synchronized, high-frequency neuronal firing. Variety of forms.	
Partial (focal) seizures	Affect single area of the brain. Most commonly originate in medial temporal lobe. Often preceded by seizure aura; can secondarily generalize. Types: ▪ Simple partial (consciousness intact)—motor, sensory, autonomic, psychic ▪ Complex partial (impaired consciousness)	Epilepsy—a disorder of recurrent seizures (febrile seizures are not epilepsy). Status epilepticus—continuous (> 5–30 min) or recurring seizures that may result in brain injury. Causes of seizures by age: ▪ Children—genetic, infection (febrile), trauma, congenital, metabolic ▪ Adults—tumor, trauma, stroke, infection ▪ Elderly—stroke, tumor, trauma, metabolic, infection
Generalized seizures	Diffuse. Types: ▪ Absence (petit mal)—3 Hz spike-and-wave discharges, no postictal confusion, blank stare ▪ Myoclonic—quick, repetitive jerks ▪ Tonic-clonic (grand mal)—alternating stiffening and movement ▪ Tonic—stiffening ▪ Atonic—“drop” seizures (falls to floor); commonly mistaken for fainting	

Headaches

Pain due to irritation of structures such as the dura, cranial nerves, or extracranial structures. More common in females, except cluster headaches.

CLASSIFICATION	LOCALIZATION	DURATION	DESCRIPTION	TREATMENT
Cluster[a]	Unilateral	15 min–3 hr; repetitive	Repetitive brief headaches. Excruciating periorbital pain with lacrimation and rhinorrhea. May present with Horner syndrome.	Acute: sumatriptan, 100% O_2 Prophylaxis: verapamil
Tension	Bilateral	> 30 min (typically 4–6 hr); constant	Steady pain. No photophobia or phonophobia. No aura.	Analgesics, NSAIDs, acetaminophen; amitriptyline for chronic pain
Migraine	Unilateral	4–72 hr	Pulsating pain with nausea, photophobia, or phonophobia. May have "aura." Due to irritation of CN V, meninges, or blood vessels (release of substance P, calcitonin gene-related peptide, vasoactive peptides).	Acute: NSAIDs, triptans, dihydroergotamine Prophylaxis: lifestyle changes (eg, sleep, exercise, diet), β-blockers, calcium channel blockers, amitriptyline, topiramate, valproate. **POUND**–**P**ulsatile, **O**ne-day duration, **U**nilateral, **N**ausea, **D**isabling

Other causes of headache include subarachnoid hemorrhage ("worst headache of my life"), meningitis, hydrocephalus, neoplasia, giant cell (temporal) arteritis.

[a] Compare with **trigeminal neuralgia**, which produces repetitive, unilateral, shooting pain in the distribution of CN V that lasts (typically) for < 1 minute (note: first-line therapy is carbamazepine).

Movement disorders

DISORDER	PRESENTATION	CHARACTERISTIC LESION	NOTES
Akathisia	Restlessness and intense urge to move		Can be seen with neuroleptic use or in Parkinson disease.
Asterixis	Extension of wrists causes "flapping" motion		Associated with hepatic encephalopathy, Wilson disease, and other metabolic derangements.
Athetosis	Slow, snake-like, writhing movements; especially seen in the fingers	Basal ganglia	
Chorea	Sudden, jerky, purposeless movements	Basal ganglia	*Chorea* = dancing. Sydenham chorea seen in acute rheumatic fever.
Dystonia	Sustained, involuntary muscle contractions		Writer's cramp, blepharospasm, torticollis.
Essential tremor	High-frequency tremor with sustained posture (eg, outstretched arms), worsened with movement or when anxious		Often familial. Patients often self-medicate with alcohol, which ↓ tremor amplitude. Treatment: nonselective β-blockers (eg, propranolol), primidone.
Hemiballismus	Sudden, wild flailing of 1 arm +/– ipsilateral leg	Contralateral subthalamic nucleus (eg, lacunar stroke)	Pronounce "**Half**-of-body **ball**istic." Contralateral lesion.
Intention tremor	Slow, zigzag motion when pointing/extending toward a target	Cerebellar dysfunction	
Myoclonus	Sudden, brief, uncontrolled muscle contraction		Jerks; hiccups; common in metabolic abnormalities such as renal and liver failure.
Resting tremor	Uncontrolled movement of distal appendages (most noticeable in hands); tremor alleviated by intentional movement	Substantia nigra (**Park**inson disease)	Occurs at rest; "pill-rolling tremor" of Parkinson disease. When you **park** your car, it is at **rest**.

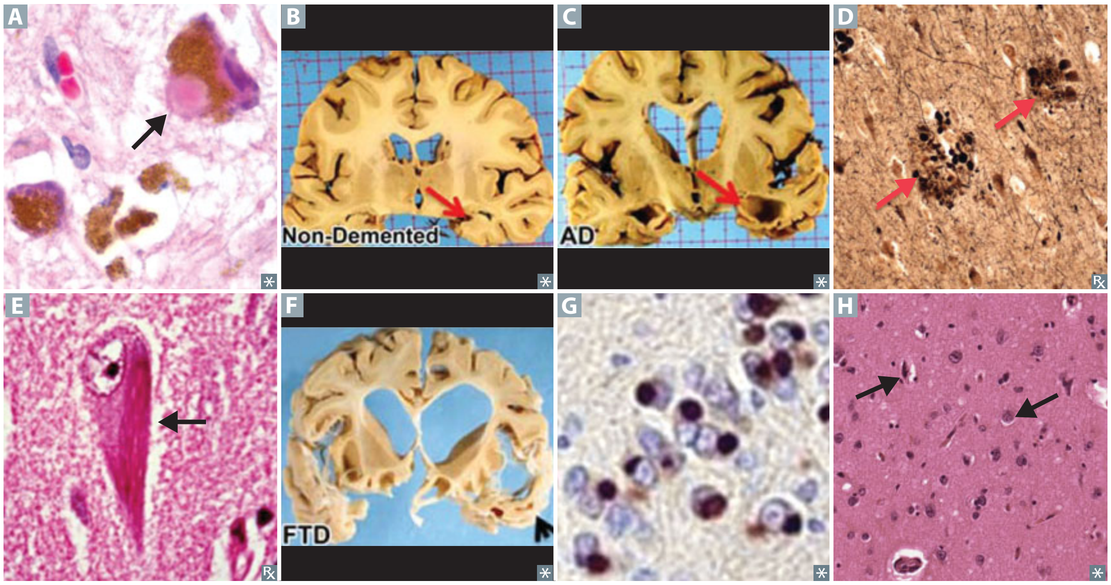
Neurodegenerative disorders

↓ in cognitive ability, memory, or function with intact consciousness.

DISEASE	DESCRIPTION	HISTOLOGIC/GROSS FINDINGS
Parkinson disease	Parkinson **TRAPS** your body: **T**remor (pill-rolling tremor at rest) **R**igidity (cogwheel) **A**kinesia (or bradykinesia) **P**ostural instability **S**huffling gait MPTP, a contaminant in illegal drugs, is metabolized to MPP+, which can cause parkinsonian symptoms.	Loss of dopaminergic neurons (ie, depigmentation) of substantia nigra pars compacta. Lewy bodies: composed of α-synuclein (intracellular eosinophilic inclusions A).
Huntington disease	Autosomal dominant trinucleotide $(CAG)_n$ repeat disorder on chromosome 4. Symptoms manifest between ages 20 and 50: chorea, athetosis, aggression, depression, dementia (sometimes initially mistaken for substance abuse). Anticipation results from expansion of **CAG** repeats. **C**audate loses **A**Ch and **G**ABA.	Atrophy of caudate and putamen with ex vacuo ventriculomegaly. ↑ dopamine, ↓ GABA, ↓ ACh in brain. Neuronal death via NMDA-R binding and glutamate excitotoxicity.
Alzheimer disease	Most common cause of dementia in elderly. Down syndrome patients have ↑ risk of developing Alzheimer disease, as APP is located on chromosome 21. Associated with the following altered proteins: ▪ ApoE2: ↓ risk of sporadic form ▪ ApoE4: ↑ risk of sporadic form ▪ APP, presenilin-1, presenilin-2: familial forms (10%) with earlier onset ↓ ACh	Widespread cortical atrophy (normal cortex B; cortex in Alzheimer disease C), especially hippocampus (arrows in B and C). Narrowing of gyri and widening of sulci. Senile plaques D in gray matter: extracellular β-amyloid core; may cause amyloid angiopathy → intracranial hemorrhage; Aβ (amyloid-β) synthesized by cleaving amyloid precursor protein (APP). Neurofibrillary tangles E: intracellular, hyperphosphorylated tau protein = insoluble cytoskeletal elements; number of tangles correlates with degree with dementia.
Frontotemporal dementia (Pick disease)	Early changes in personality and behavior (behavioral variant), or aphasia (primary progressive aphasia). May have associated movement disorders (eg, parkinsonism, ALS-like UMN/LMN degeneration).	Frontotemporal lobe degeneration F. Inclusions of hyperphosphorylated tau (round Pick bodies G) or ubiquitinated TDP-43.
Lewy body dementia	Dementia and visual hallucinations (“ha**Lewy**cinations”) → parkinsonian features	Intracellular Lewy bodies A primarily in cortex.

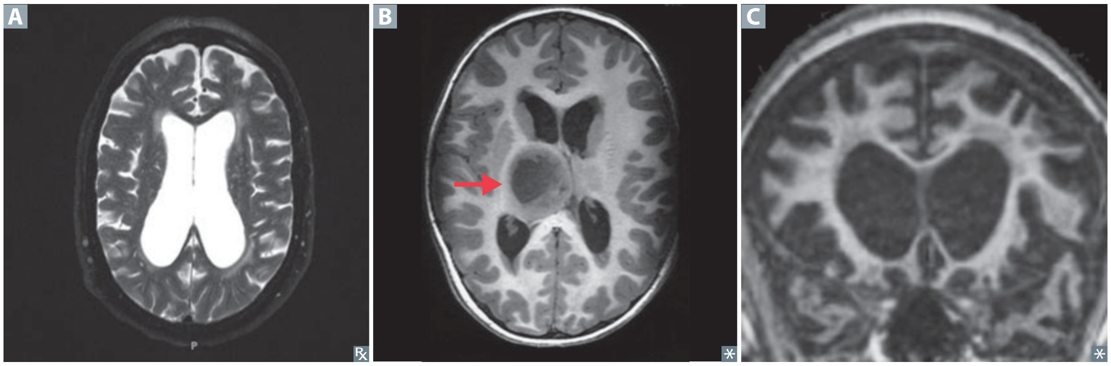
Neurodegenerative disorders *(continued)*

DISEASE	DESCRIPTION	HISTOLOGIC/GROSS FINDINGS
Vascular dementia	Result of multiple arterial infarcts and/or chronic ischemia. Step-wise decline in cognitive ability with late-onset memory impairment. 2nd most common cause of dementia in elderly.	MRI or CT shows multiple cortical and/or subcortical infarcts.
Creutzfeldt-Jakob disease	Rapidly progressive (weeks to months) dementia with myoclonus ("startle myoclonus"). Commonly see periodic sharp waves on EEG and ↑ 14-3-3 protein in CSF.	Spongiform cortex. Prions ($\text{PrP}^{\text{c}} \rightarrow \text{PrP}^{\text{sc}}$ sheet [β-pleated sheet resistant to proteases]) H.

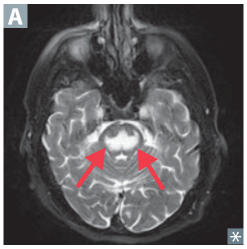


Idiopathic intracranial hypertension (pseudotumor cerebri)	↑ ICP with no apparent cause on imaging (eg, hydrocephalus, obstruction of CSF outflow). Risk factors include female gender, obesity, vitamin A excess, tetracycline, danazol. Findings: headache, diplopia (usually from CN VI palsy), no change in mental status. Papilledema seen on fundoscopy. Lumbar puncture reveals ↑ opening pressure and provides headache relief. Treatment: weight loss, acetazolamide, topiramate, invasive procedures for refractory cases (eg, repeat lumbar puncture, CSF shunt placement, optic nerve sheath fenestration surgery).

Hydrocephalus	↑ CSF volume → ventricular dilation +/– ↑ ICP.
Communicating	
Communicating hydrocephalus	↓ CSF absorption by arachnoid granulations (eg, arachnoid scarring post-meningitis) → ↑ ICP, papilledema, herniation.
Normal pressure hydrocephalus	Affects the elderly; idiopathic; CSF pressure elevated only episodically; does not result in increased subarachnoid space volume. Expansion of ventricles A distorts the fibers of the corona radiata → triad of **urinary incontinence**, **ataxia**, and **cognitive dysfunction** (sometimes reversible). "**Wet**, **wobbly**, and **wacky**." Characteristic magnetic gait (feet appear stuck to floor).
Noncommunicating (obstructive)	
Noncommunicating hydrocephalus	Caused by structural blockage of CSF circulation within ventricular system (eg, stenosis of aqueduct of Sylvius; colloid cyst blocking foramen of Monro; tumor B).
Hydrocephalus mimics	
Ex vacuo ventriculomegaly	Appearance of ↑ CSF on imaging C, but is actually due to decreased brain tissue and neuronal atrophy (eg, Alzheimer disease, advanced HIV, Pick disease, Huntington disease). ICP is normal; triad is not seen.



Osmotic demyelination syndrome (central pontine myelinolysis)



Acute paralysis, dysarthria, dysphagia, diplopia, loss of consciousness. Can cause "locked-in syndrome." Massive axonal demyelination in pontine white matter A 2° to osmotic changes. Commonly iatrogenic, caused by overly rapid correction of hyponatremia. In contrast, correcting hypernatremia too quickly results in cerebral edema/herniation.

Correcting serum Na^+ too fast:

- "From low to high, your pons will die" (osmotic demyelination syndrome)
- "From high to low, your brain will blow" (cerebral edema/herniation)

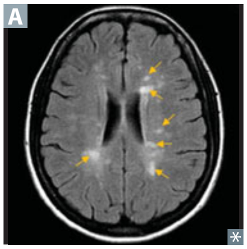
Multiple sclerosis

Autoimmune inflammation and demyelination of CNS (brain and spinal cord). Patients can present with optic neuritis (sudden loss of vision resulting in Marcus Gunn pupils), INO, hemiparesis, hemisensory symptoms, bladder/bowel dysfunction. Symptoms may exacerbate with increased body temperature (eg, hot bath, exercise). Relapsing and remitting is most common clinical course. Most often affects women in their 20s and 30s; more common in Caucasians living farther from equator. Neck flexion may precipitate sensation of electric shock running down spine (Lhermitte phenomenon).

Charcot triad of MS is a **SIN**:

- **S**canning speech
- **I**ntention tremor (also **I**ncontinence and **I**nternuclear ophthalmoplegia)
- **N**ystagmus

FINDINGS



↑ IgG level and myelin basic protein in CSF. Oligoclonal bands are diagnostic. MRI is gold standard. Periventricular plaques A (areas of oligodendrocyte loss and reactive gliosis) with preservation of axons. Multiple white matter lesions disseminated in space and time.

TREATMENT

Slow progression with disease-modifying therapies (eg, β-interferon, glatiramer, natalizumab). Treat acute flares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, GABA_B receptor agonists), pain (TCAs, anticonvulsants).

Acute inflammatory demyelinating polyradiculopathy

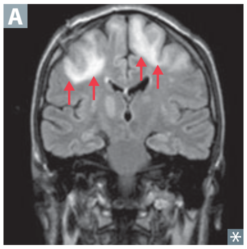
Most common subtype of Guillain-Barré syndrome. Autoimmune condition that destroys Schwann cells → inflammation and demyelination of peripheral nerves and motor fibers. Results in symmetric ascending muscle weakness/paralysis and depressed tendon reflexes beginning in lower extremities. Facial paralysis in 50% of cases. May see autonomic dysregulation (eg, cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Almost all patients survive; the majority recover completely after weeks to months.

↑ CSF protein with normal cell count (albuminocytologic dissociation). ↑ protein may cause papilledema.

Associated with infections (eg, *Campylobacter jejuni*, viral) → autoimmune attack of peripheral myelin due to molecular mimicry, inoculations, and stress, but no definitive link to pathogens.

Respiratory support is critical until recovery. Additional treatment: plasmapheresis, IV immunoglobulins. No role for steroids.

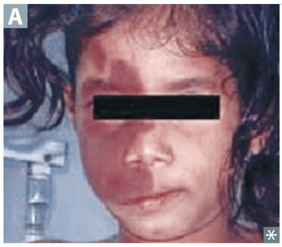
Other demyelinating and dysmyelinating diseases

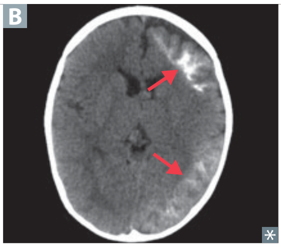
Acute disseminated (postinfectious) encephalomyelitis	Multifocal inflammation and demyelination after infection or vaccination. Presents with rapidly progressive multifocal neurologic symptoms, altered mental status.
Charcot-Marie-Tooth disease	Also known as hereditary motor and sensory neuropathy (HMSN). Group of progressive hereditary nerve disorders related to the defective production of proteins involved in the structure and function of peripheral nerves or the myelin sheath. Typically autosomal dominant inheritance pattern and associated with foot deformities (eg, pes cavus, hammer toe), lower extremity weakness (eg, foot drop) and sensory deficits.
Krabbe disease	Autosomal recessive lysosomal storage disease due to deficiency of galactocerebrosidase. Buildup of galactocerebroside and psychosine destroys myelin sheath. Findings: peripheral neuropathy, developmental delay, optic atrophy, globoid cells.
Metachromatic leukodystrophy	Autosomal recessive lysosomal storage disease, most commonly due to arylsulfatase A deficiency. Buildup of sulfatides → impaired production and destruction of myelin sheath. Findings: central and peripheral demyelination with ataxia, dementia.
Progressive multifocal leukoencephalopathy 	Demyelination of CNS A due to destruction of oligodendrocytes. Seen in 2–4% of AIDS patients (reactivation of latent JC virus infection). Rapidly progressive, usually fatal. ↑ risk associated with natalizumab, rituximab.

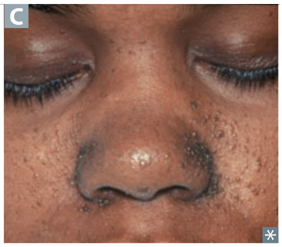
Adrenoleukodystrophy	X-linked genetic disorder typically affecting males. Disrupts metabolism of very-long-chain fatty acids → excessive buildup in nervous system, adrenal gland, testes. Progressive disease that can lead to long-term coma/death and adrenal gland crisis.

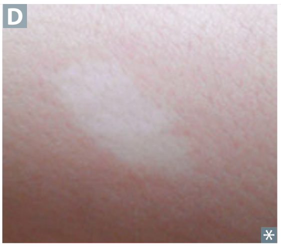
Neurocutaneous disorders

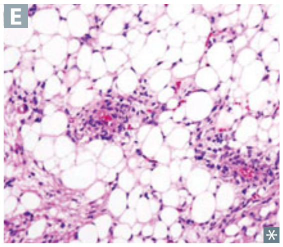
Sturge-Weber syndrome (encephalotrigeminal angiomatosis)	Congenital, noninherited (sporadic), developmental anomaly of neural crest derivatives due to somatic mosaicism for an activating mutation in one copy of the *GNAQ* gene. Affects small (capillary-sized) blood vessels → port-wine stain of the face A (nevus flammeus, a non-neoplastic "birthmark" in CN V_1/V_2 distribution); ipsilateral leptomeningeal angioma B → seizures/epilepsy; intellectual disability; and episcleral hemangioma → ↑ IOP → early-onset glaucoma. STURGE-Weber: Sporadic, port-wine Stain; Tram track calcifications (opposing gyri); Unilateral; Retardation (intellectual disability); Glaucoma, *GNAQ* gene; Epilepsy.
Tuberous sclerosis	*TSC1*/*TSC2* mutation on chromosome 16. Autosomal dominant, variable expression. HAMARTOMAS: Hamartomas in CNS and skin; Angiofibromas C; Mitral regurgitation; Ash-leaf spots D; cardiac Rhabdomyoma; (Tuberous sclerosis); autosomal dOminant; Mental retardation (intellectual disability); renal Angiomyolipoma E; Seizures, Shagreen patches. ↑ incidence of subependymal giant cell astrocytomas and ungual fibromas.
Neurofibromatosis type I (von Recklinghausen disease)	Mutation in *NF1* tumor suppressor gene on chromosome 17 (17 letters in "von Recklinghausen"), which normally codes for neurofibromin, a negative regulator of RAS. Autosomal dominant, 100% penetrance. Café-au-lait spots F, cutaneous neurofibromas G, optic gliomas, pheochromocytomas, Lisch nodules (pigmented iris hamartomas H).
Neurofibromatosis type II	Mutation in *NF2* tumor suppressor gene on chromosome 22. Autosomal dominant. Findings: bilateral acoustic schwannomas, juvenile cataracts, meningiomas, and ependymomas. NF2 affects 2 ears, 2 eyes, and 2 parts of the brain.
von Hippel-Lindau disease	Deletion of *VHL* gene on chromosome 3p (VHL = 3 letters). Autosomal dominant. Characterized by development of numerous tumors, both benign and malignant. HARP: Hemangioblastomas (high vascularity with hyperchromatic nuclei I) in retina, brain stem, cerebellum, spine J; Angiomatosis (eg, cavernous hemangiomas in skin, mucosa, organs); bilateral Renal cell carcinomas; Pheochromocytomas.

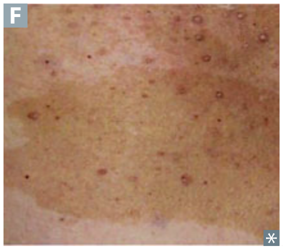


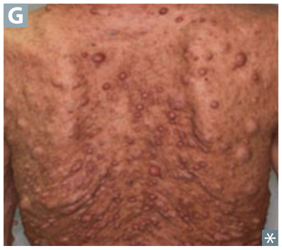


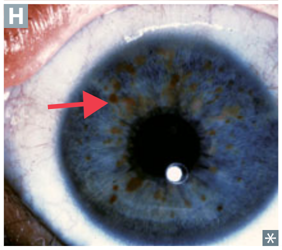


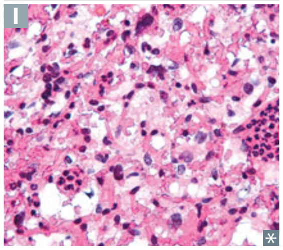


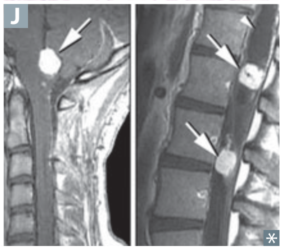










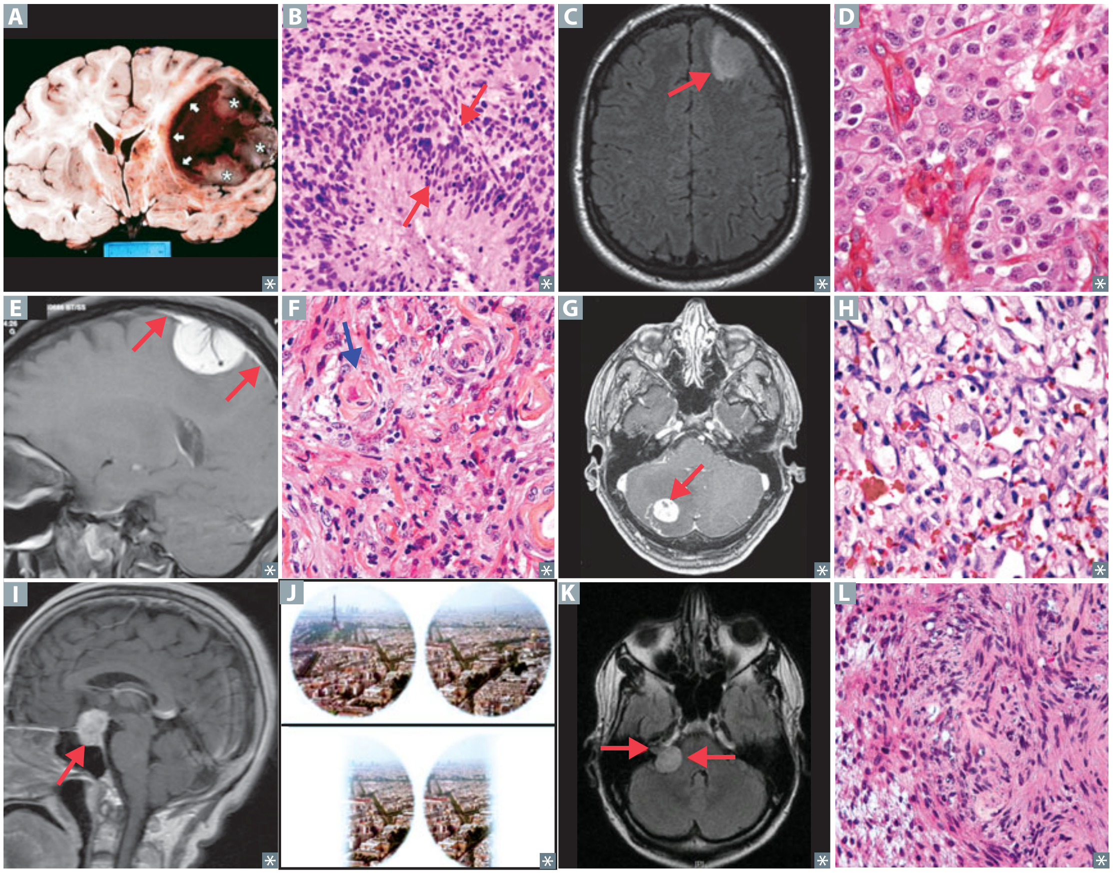


Adult primary brain tumors

TUMOR	DESCRIPTION	HISTOLOGY
Glioblastoma multiforme (grade IV astrocytoma)	Common, highly malignant 1° brain tumor with ~ 1-year median survival. Found in cerebral hemispheres A. Can cross corpus callosum ("butterfly glioma").	Astrocyte origin, GFAP ⊕. "Pseudopalisading" pleomorphic tumor cells B border central areas of necrosis and hemorrhage.
Oligodendroglioma	Relatively rare, slow growing. Most often in frontal lobes C. "Chicken-wire" capillary pattern.	Oligodendrocyte origin. "Fried egg" cells—round nuclei with clear cytoplasm D. Often calcified.
Meningioma	Common, typically benign 1° brain tumor. Most often occurs near surfaces of brain and in parasagittal region. Extra-axial (external to brain parenchyma) and may have a dural attachment ("tail" E). Often asymptomatic; may present with seizures or focal neurologic signs. Resection and/or radiosurgery.	Arachnoid cell origin. Spindle cells concentrically arranged in a whorled pattern; psammoma bodies F (laminated calcifications).
Hemangioblastoma	Most often cerebellar G. Associated with von Hippel-Lindau syndrome when found with retinal angiomas. Can produce erythropoietin → 2° polycythemia.	Blood vessel origin. Closely arranged, thin-walled capillaries with minimal intervening parenchyma H.
Pituitary adenoma	Adenoma may be nonfunctioning or hyperfunctioning. Most commonly from lactotrophs (prolactinoma) I → hyperprolactinemia; less commonly adenoma of somatotrophs (GH) → acromegaly/gigantism; corticotrophs (ACTH) → Cushing's disease. Rarely, adenoma of thyrotrophs (TSH) and gonadotroph (FSH, LH). Bitemporal hemianopia due to pressure on optic chiasm (J shows normal visual field above, patient's perspective below). Sequelae include hyper- or hypopituitarism, which may be caused by pituitary apoplexy.	Hyperplasia of only one type of endocrine cells found in pituitary (ie, lactotroph, gonadotroph, somatotroph, corticotroph).
Schwannoma	Classically at the cerebellopontine angle K, but can be along any peripheral nerve. Often localized to CN VIII in internal acoustic meatus → vestibular schwannoma. Bilateral vestibular schwannomas found in NF-2. Resection or stereotactic radiosurgery.	Schwann cell origin L, S-100 ⊕.

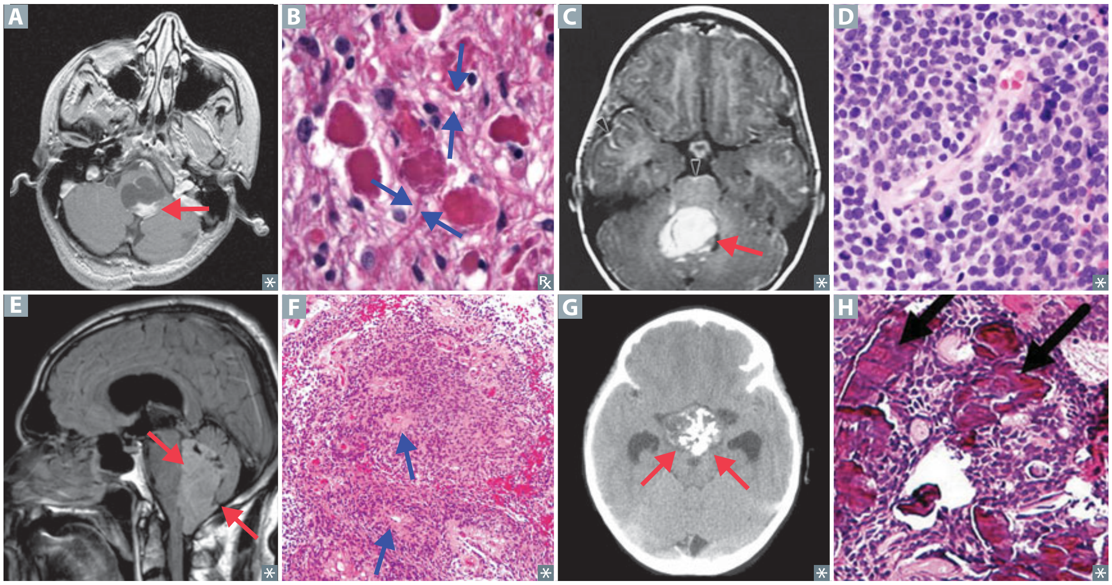
Adult primary brain tumors *(continued)*

TUMOR	DESCRIPTION	HISTOLOGY

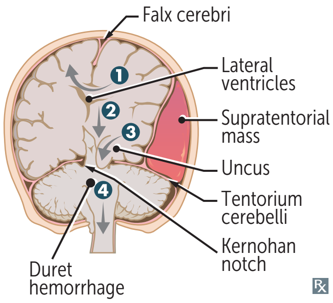


Childhood primary brain tumors

TUMOR	DESCRIPTION	HISTOLOGY
Pilocytic (low-grade) astrocytoma	Usually well circumscribed. In children, most often found in posterior fossa A (eg, cerebellum). May be supratentorial. Benign; good prognosis.	Glial cell origin, GFAP ⊕. Rosenthal fibers—eosinophilic, corkscrew fibers B. Cystic + solid (gross).
Medulloblastoma	Most common malignant brain tumor in childhood. Commonly involves cerebellum C. Can compress 4th ventricle, causing noncommunicating hydrocephalus. Can send "drop metastases" to spinal cord.	Form of primitive neuroectodermal tumor (PNET). Homer-Wright rosettes, small blue cells D.
Ependymoma	Most commonly found in 4th ventricle E. Can cause hydrocephalus. Poor prognosis.	Ependymal cell origin. Characteristic perivascular rosettes F. Rod-shaped blepharoplasts (basal ciliary bodies) found near the nucleus.
Craniopharyngioma	Most common childhood supratentorial tumor. May be confused with pituitary adenoma (both cause bitemporal hemianopia).	Derived from remnants of Rathke pouch. Calcification is common G H. Cholesterol crystals found in "motor oil"—like fluid within tumor.
Pinealoma	Tumor of pineal gland. Can cause Parinaud syndrome (compression of tectum → vertical gaze palsy); obstructive hydrocephalus (compression of cerebral aqueduct); precocious puberty in males (β-hCG production).	Similar to germ cell tumors (eg, testicular seminoma).



Herniation syndromes

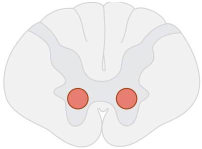
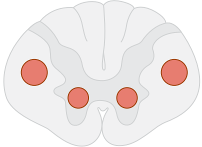
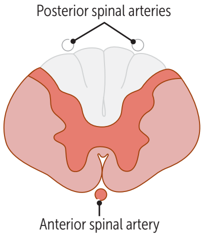
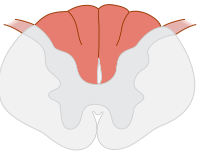
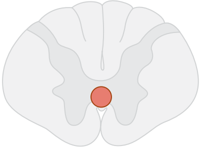
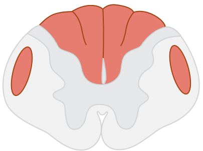


① Cingulate (subfalcine) herniation under falx cerebri	Can compress anterior cerebral artery.
② Transtentorial (central/downward) herniation	Caudal displacement of brain stem → rupture of paramedian basilar artery branches → Duret hemorrhages. Usually fatal.
③ Uncal herniation	Uncus = medial temporal lobe. Compresses ipsilateral CN III (blown pupil, "down-and-out" gaze), ipsilateral PCA (contralateral homonymous hemianopia with macular sparing), contralateral crus cerebri at the Kernohan notch (ipsilateral paresis; a "false localization" sign).
④ Cerebellar tonsillar herniation into the foramen magnum	Coma and death result when these herniations compress the brain stem.

Motor neuron signs

SIGN	UMN LESION	LMN LESION	COMMENTS
Weakness	+	+	**Lower** motor neuron = everything **lower**ed (less muscle mass, ↓ muscle tone, ↓ reflexes, downgoing toes). **U**pper motor neuron = everything **up** (tone, DTRs, toes). Fasciculations = muscle twitching. Positive Babinski is normal in infants.
Atrophy	–	+	
Fasciculations	–	+	
Reflexes	↑	↓	
Tone	↑	↓	
Babinski	+	–	
Spastic paresis	+	–	
Flaccid paralysis	–	+	
Clasp knife spasticity	+	–	

Spinal cord lesions

AREA AFFECTED	DISEASE	CHARACTERISTICS
	Poliomyelitis and Werdnig-Hoffmann disease	Congenital degeneration of anterior horns of spinal cord. LMN lesions only. "Floppy baby" with marked hypotonia and tongue fasciculations. Infantile type has median age of death of 7 months. Autosomal recessive inheritance. Poliomyelitis → asymmetric weakness. Werdnig-Hoffmann disease → symmetric weakness.
	Amyotrophic lateral sclerosis	Combined UMN and LMN deficits with no sensory or bowel/bladder deficits (due to loss of cortical and spinal cord motor neurons, respectively). Can be caused by defect in superoxide dismutase 1. Commonly presents with asymmetric limb weakness (hands/feet), fasciculations, eventual atrophy. Fatal. Commonly known as Lou Gehrig disease. Treatment: riluzole.
	Complete occlusion of anterior spinal artery	Spares dorsal columns and Lissauer tract; mid-thoracic ASA territory is watershed area, as artery of Adamkiewicz supplies ASA below ~ T8. Presents with UMN deficit below the lesion (corticospinal tract), LMN deficit at the level of the lesion (anterior horn), and loss of pain and temperature sensation below the lesion (spinothalamic tract).
	Tabes dorsalis	Caused by 3° syphilis. Results from degeneration (demyelination) of dorsal columns and roots → progressive sensory ataxia (impaired proprioception → poor coordination). Associated with Charcot joints, shooting pain, Argyll Robertson pupils. Exam will demonstrate absence of DTRs and ⊕ Romberg sign.
	Syringomyelia	Syrinx expands and damages anterior white commissure of spinothalamic tract (2nd-order neurons) → bilateral loss of pain and temperature sensation in cape-like distribution; seen with Chiari I malformation; can expand and affect other tracts.
	Vitamin B_{12} deficiency	Subacute combined degeneration (SCD)—demyelination of Spinocerebellar tracts, lateral Corticospinal tracts, and Dorsal columns. Ataxic gait, paresthesia, impaired position/vibration sense.
	Cauda equina syndrome	Unilateral symptoms including radicular pain, absent knee and ankle reflex, loss of bladder and anal sphincter control. Can cause saddle anesthesia. Treatment: emergent surgery and steroids. Due to compression of spinal roots from L2 and below, often caused by intravertebral disk herniation or tumors.

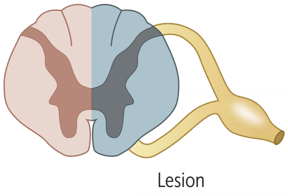
Poliomyelitis

Caused by poliovirus (fecal-oral transmission). Replicates in oropharynx and small intestine before spreading via bloodstream to CNS. Infection causes destruction of cells in anterior horn of spinal cord (LMN death).

Signs of LMN lesion: asymmetric weakness, hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Respiratory muscle involvement leads to respiratory failure. Signs of infection: malaise, headache, fever, nausea, etc.

CSF shows ↑ WBCs (lymphocytic pleocytosis) and slight ↑ of protein (with no change in CSF glucose). Virus recovered from stool or throat.

Brown-Séquard syndrome



Hemisection of spinal cord. Findings:

❶ Ipsilateral loss of all sensation **at** level of lesion

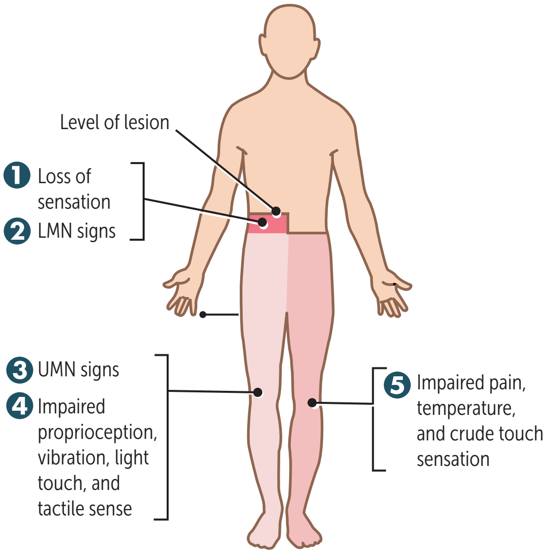
❷ Ipsilateral LMN signs (eg, flaccid paralysis) **at** level of lesion

❸ Ipsilateral UMN signs **below** level of lesion (due to corticospinal tract damage)

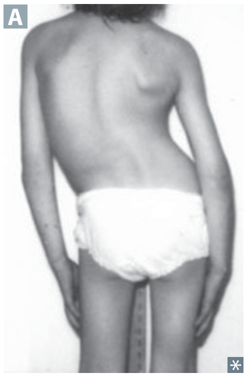
❹ Ipsilateral loss of proprioception, vibration, light (2-point discrimination) touch, and tactile sense **below** level of lesion (due to dorsal column damage).

❺ Contralateral pain, temperature, and crude (non-discriminative) touch **below** level of lesion (due to spinothalamic tract damage)

If lesion occurs above T1, patient may present with ipsilateral Horner syndrome due to damage of oculosympathetic pathway.


Level of lesion
❶ Loss of sensation
❷ LMN signs
❸ UMN signs
❹ Impaired proprioception, vibration, light touch, and tactile sense
❺ Impaired pain, temperature, and crude touch sensation

Friedreich ataxia



Autosomal recessive trinucleotide repeat disorder **(GAA)**$_n$ on chromosome 9 in gene that encodes frataxin (iron binding protein). Leads to impairment in mitochondrial functioning. Degeneration of multiple spinal cord tracts → muscle weakness and loss of DTRs, vibratory sense, proprioception. **Staggering** gait, frequent **falling**, nystagmus, dysarthria, pes cavus, hammer toes, **diabetes** mellitus, **hypertrophic cardiomyopathy** (cause of death). Presents in childhood with kyphoscoliosis A.

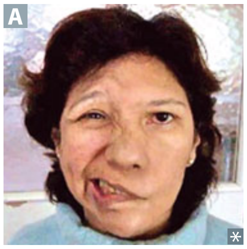
Friedreich is **F**ratastic (**frataxin**): he's your favorite **frat** brother, always **staggering** and **falling** but has a **sweet**, **big heart**.

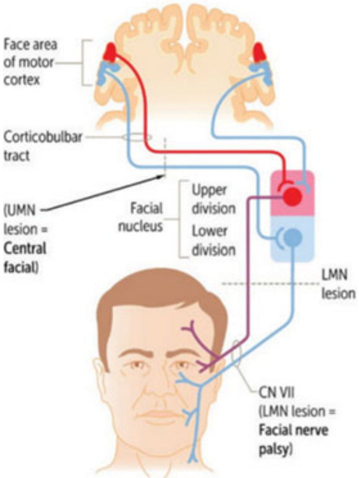
Ataxic **GAA**it.

Common cranial nerve lesions

CN V motor lesion	Jaw deviates **toward** side of lesion due to unopposed force from the opposite pterygoid muscle.
CN X lesion	Uvula deviates **away** from side of lesion. Weak side collapses and uvula points away.
CN XI lesion	Weakness turning head to contralateral side of lesion (SCM). Shoulder droop on side of lesion (trapezius). The left SCM contracts to help turn the head to the right.
CN XII lesion	LMN lesion. Tongue deviates **toward** side of lesion ("lick your wounds") due to weakened tongue muscles on affected side.

Facial nerve lesions

Upper motor neuron lesion	Destruction of motor cortex or connection between motor cortex and facial nucleus in pons → contralateral paralysis of lower muscles of facial expression. Forehead is spared due to its bilateral UMN innervation.
Lower motor neuron lesion  	Destruction of facial nucleus or CN VII anywhere along its course → ipsilateral paralysis of upper and lower muscles of facial expression A, hyperacusis, loss of taste sensation to anterior tongue. When idiopathic (most common), facial nerve palsy is called Bell palsy. May also be caused by Lyme disease, herpes simplex, herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors (eg, parotid gland), diabetes mellitus. Treatment is corticosteroids, acyclovir. Most patients gradually recover function.


Face area of motor cortex
Corticobulbar tract
(UMN lesion = Central facial)
Facial nucleus
Upper division
Lower division
LMN lesion
CN VII (LMN lesion = Facial nerve palsy)

▶ NEUROLOGY—OTOLOGY

Auditory physiology

Outer ear	Visible portion of ear (pinna), includes auditory canal and eardrum. Transfers sound waves via vibration of eardrum.
Middle ear	Air-filled space with three bones called the ossicles (malleus, incus, stapes). Ossicles conduct and amplify sound from eardrum to inner ear.
Inner ear	Snail-shaped, fluid-filled cochlea. Contains basilar membrane that vibrates 2° to sound waves. Vibration transduced via specialized hair cells → auditory nerve signaling → brain stem. Each frequency leads to vibration at specific location on basilar membrane (tonotopy): ▪ Low frequency heard at apex near helicotrema (wide and flexible). ▪ High frequency heard best at base of cochlea (thin and rigid).

Diagnosing hearing loss

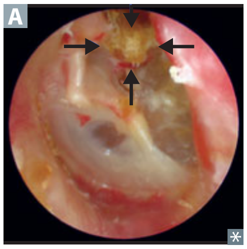
	RINNE TEST	WEBER TEST
Conductive	Abnormal (bone > air)	Localizes to affected ear
Sensorineural	Normal (air > bone)	Localizes to unaffected ear

Types of hearing loss

Noise-induced	Damage to stereociliated cells in organ of Corti. Loss of high-frequency hearing first. Sudden extremely loud noises can produce hearing loss due to tympanic membrane rupture.
Presbycusis	Aging-related sensorineural hearing loss (often of higher frequencies) due to destruction of hair cells at the cochlear base (preserved low-frequency hearing at apex).

Cholesteatoma

Overgrowth of desquamated keratin debris within the middle ear space (A, arrows); may erode ossicles, mastoid air cells → conductive hearing loss.



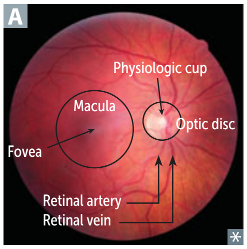
Vertigo

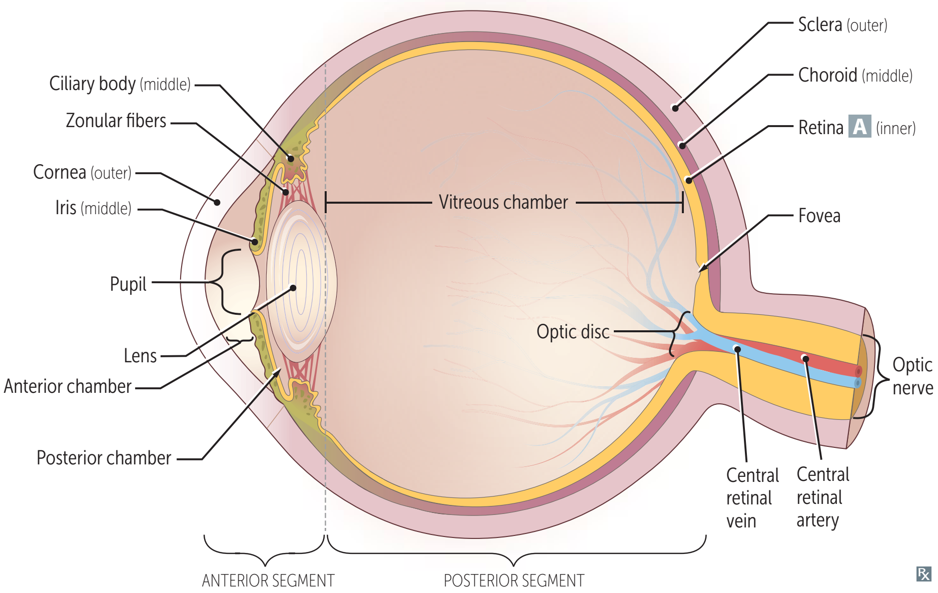
Sensation of spinning while actually stationary. Subtype of "dizziness," but distinct from "lightheadedness."

Peripheral vertigo	More common. Inner ear etiology (eg, semicircular canal debris, vestibular nerve infection, Ménière disease, benign paroxysmal positional vertigo). Positional testing → delayed horizontal nystagmus.
Central vertigo	Brain stem or cerebellar lesion (eg, stroke affecting vestibular nuclei or posterior fossa tumor). Findings: directional or purely vertical nystagmus, skew deviation, diplopia, dysmetria. Positional testing → immediate nystagmus in any direction; may change directions. Focal neurologic findings.

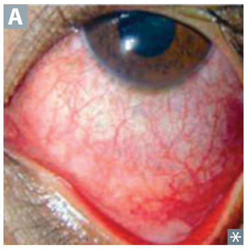
▸ NEUROLOGY—OPHTHALMOLOGY

Normal eye


A
Physiologic cup
Macula
Optic disc
Fovea
Retinal artery
Retinal vein


Sclera (outer)
Choroid (middle)
Retina A (inner)
Fovea
Ciliary body (middle)
Zonular fibers
Cornea (outer)
Iris (middle)
Vitreous chamber
Pupil
Optic disc
Lens
Anterior chamber
Posterior chamber
Optic nerve
Central retinal vein
Central retinal artery
ANTERIOR SEGMENT
POSTERIOR SEGMENT

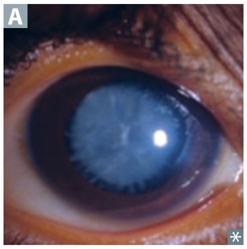
Conjunctivitis



Inflammation of the conjunctiva → red eye **A**.
Allergic—itchy eyes, bilateral.
Bacterial—pus; treat with antibiotics.
Viral—most common, often adenovirus; sparse mucous discharge, swollen preauricular node; self-resolving.

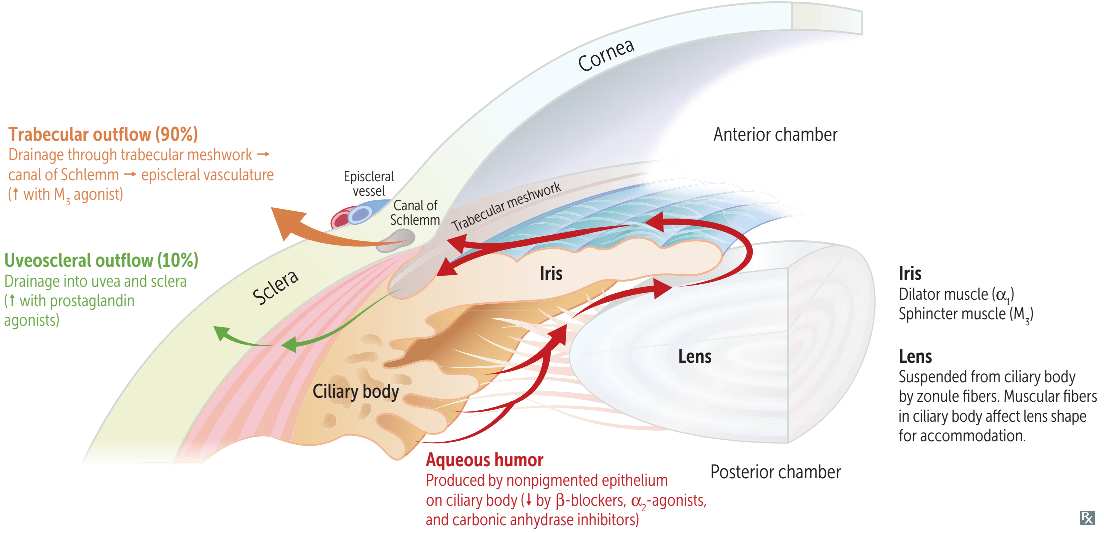
Refractive errors	Common cause of impaired vision, correctable with glasses.
Hyperopia	Also known as “farsightedness.” Eye too short for refractive power of cornea and lens → light focused behind retina. Correct with convex (converging) lenses.
Myopia	Also known as “nearsightedness.” Eye too long for refractive power of cornea and lens → light focused in front of retina. Correct with concave (diverging) lens.
Astigmatism	Abnormal curvature of cornea → different refractive power at different axes. Correct with cylindrical lens.
Presbyopia	Aging-related impaired accommodation (focusing on near objects), primarily due to ↓ lens elasticity, changes in lens curvature, ↓ strength of the ciliary muscle. Patients often need “reading glasses” (magnifiers).

Cataract



Painless, often bilateral, opacification of lens A, often resulting in ↓ vision. Acquired risk factors: ↑ age, smoking, excessive alcohol use, excessive sunlight, prolonged corticosteroid use, diabetes mellitus, trauma, infection; congenital risk factors: classic galactosemia, galactokinase deficiency, trisomies (13, 18, 21), ToRCHeS infections (eg, rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.

Aqueous humor pathway


Cornea
Anterior chamber
Trabecular outflow (90%)
Drainage through trabecular meshwork → canal of Schlemm → episcleral vasculature (↑ with M_3 agonist)
Episcleral vessel
Canal of Schlemm
Trabecular meshwork
Uveoscleral outflow (10%)
Drainage into uvea and sclera (↑ with prostaglandin agonists)
Sclera
Iris
Ciliary body
Lens
Iris
Dilator muscle (α_1)
Sphincter muscle (M_3)
Lens
Suspended from ciliary body by zonule fibers. Muscular fibers in ciliary body affect lens shape for accommodation.
Aqueous humor
Produced by nonpigmented epithelium on ciliary body (↓ by β-blockers, α_2-agonists, and carbonic anhydrase inhibitors)
Posterior chamber

Glaucoma

Optic disc atrophy with characteristic cupping (thinning of outer rim of optic nerve head B versus normal A), usually with elevated intraocular pressure (IOP) and progressive peripheral visual field loss if untreated. Treatment is through pharmacologic or surgical lowering of the IOP.

Open-angle glaucoma

Associated with ↑ age, African-American race, family history. Painless, more common in US.

Primary—cause unclear.

Secondary—blocked trabecular meshwork from WBCs (eg, uveitis), RBCs (eg, vitreous hemorrhage), retinal elements (eg, retinal detachment).

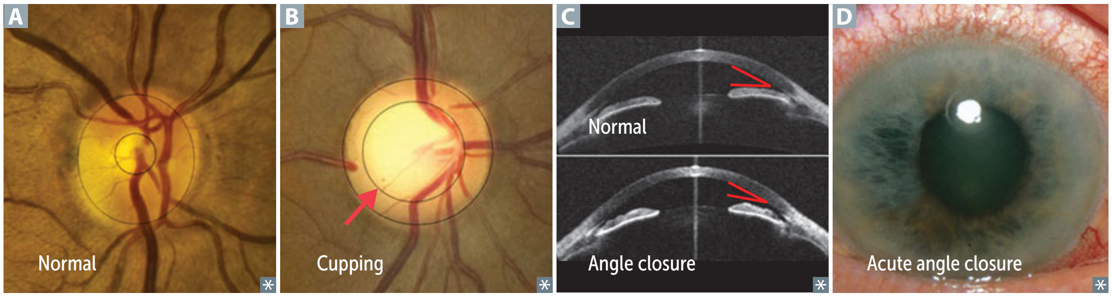
Closed- or narrow-angle glaucoma

Primary—enlargement or forward movement of lens against central iris (pupil margin) → obstruction of normal aqueous flow through pupil → fluid builds up behind iris, pushing peripheral iris against cornea C and impeding flow through trabecular meshwork.

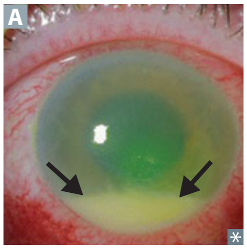
Secondary—hypoxia from retinal disease (eg, diabetes mellitus, vein occlusion) induces vasoproliferation in iris that contracts angle.

Chronic closure—often asymptomatic with damage to optic nerve and peripheral vision.

Acute closure—true ophthalmic emergency. ↑ IOP pushes iris forward → angle closes abruptly. Very painful, red eye D, sudden vision loss, halos around lights, frontal headache, fixed and mid-dilated pupil. Do not give epinephrine because of its mydriatic effect.

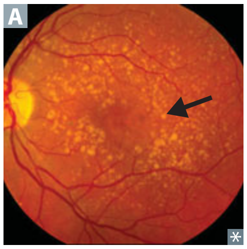


Uveitis



Inflammation of uvea; specific name based on location within affected eye. Anterior uveitis: iritis; posterior uveitis: choroiditis and/or retinitis. May have hypopyon (accumulation of pus in anterior chamber A) or conjunctival redness. Associated with systemic inflammatory disorders (eg, sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, HLA-B27–associated conditions).

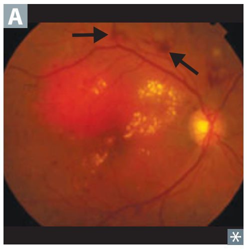
Age-related macular degeneration



Degeneration of macula (central area of retina). Causes distortion (metamorphopsia) and eventual loss of central vision (scotomas).

- Dry (nonexudative, > 80%)—Deposition of yellowish extracellular material in between Bruch membrane and retinal pigment epithelium ("Drusen") A with gradual ↓ in vision. Prevent progression with multivitamin and antioxidant supplements.
- Wet (exudative, 10–15%)—rapid loss of vision due to bleeding 2° to choroidal neovascularization. Treat with anti-VEGF (vascular endothelial growth factor) injections (eg, ranibizumab).

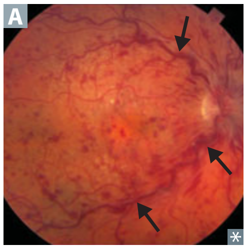
Diabetic retinopathy



Retinal damage due to chronic hyperglycemia. Two types:

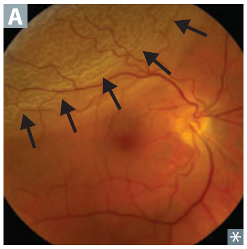
- Nonproliferative—damaged capillaries leak blood → lipids and fluid seep into retina → hemorrhages (arrows in A) and macular edema. Treatment: blood sugar control.
- Proliferative—chronic hypoxia results in new blood vessel formation with resultant traction on retina. Treatment: peripheral retinal photocoagulation, surgery, anti-VEGF.

Retinal vein occlusion



Blockage of central or branch retinal vein due to compression from nearby arterial atherosclerosis. Retinal hemorrhage and venous engorgement (arrows in A), edema in affected area.

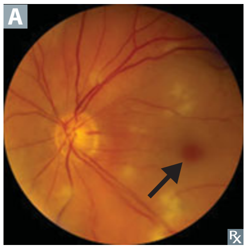
Retinal detachment



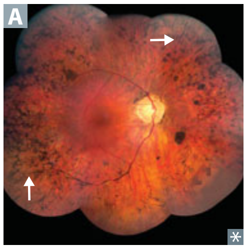
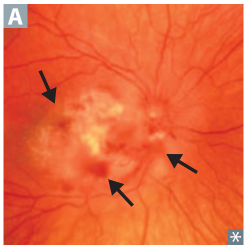
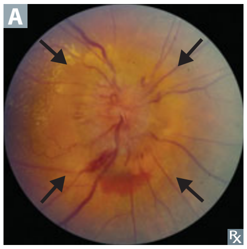
Separation of neurosensory layer of retina (photoreceptor layer with rods and cones) from outermost pigmented epithelium (normally shields excess light, supports retina) → degeneration of photoreceptors → vision loss. May be 2° to retinal breaks, diabetic traction, inflammatory effusions. Visualized on fundoscopy as crinkling of retinal tissue A and changes in vessel direction.

Breaks more common in patients with high myopia and/or history of head trauma. Often preceded by posterior vitreous detachment (“flashes” and “floaters”) and eventual monocular loss of vision like a “curtain drawn down.” Surgical emergency.

Central retinal artery occlusion



Acute, painless monocular vision loss. Retina cloudy with attenuated vessels and “cherry-red” spot at fovea (center of macula) A. Evaluate for embolic source (eg, carotid artery atherosclerosis, cardiac vegetations, patent foramen ovale).

Retinitis pigmentosa 	Inherited retinal degeneration. Painless, progressive vision loss beginning with night blindness (rods affected first). Bone spicule-shaped deposits around macula A.
Retinitis 	Retinal edema and necrosis (arrows in A) leading to scar. Often viral (CMV, HSV, VZV), but can be bacterial or parasitic. May be associated with immunosuppression.
Papilledema 	Optic disc swelling (usually bilateral) due to ↑ ICP (eg, 2° to mass effect). Enlarged blind spot and elevated optic disc with blurred margins A.

Pupillary control

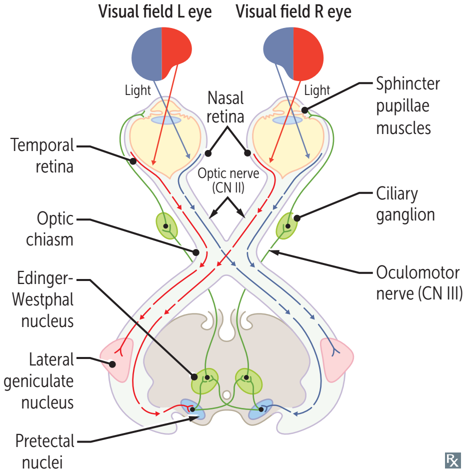
Miosis

Constriction, parasympathetic:
- 1st neuron: Edinger-Westphal nucleus to ciliary ganglion via CN III
- 2nd neuron: short ciliary nerves to sphincter pupillae muscles

Pupillary light reflex

Light in either retina sends a signal via CN II to pretectal nuclei (dashed lines in image) in midbrain that activates bilateral Edinger-Westphal nuclei; pupils contract bilaterally (consensual reflex).

Result: illumination of 1 eye results in bilateral pupillary constriction.


Visual field L eye
Visual field R eye
Light
Light
Nasal retina
Sphincter pupillae muscles
Temporal retina
Optic nerve (CN II)
Ciliary ganglion
Optic chiasm
Oculomotor nerve (CN III)
Edinger-Westphal nucleus
Lateral geniculate nucleus
Pretectal nuclei
℞

Mydriasis

Dilation, sympathetic:
- 1st neuron: hypothalamus to ciliospinal center of Budge (C8–T2)
- 2nd neuron: exit at T1 to superior cervical ganglion (travels along cervical sympathetic chain near lung apex, subclavian vessels)
- 3rd neuron: plexus along internal carotid, through cavernous sinus; enters orbit as long ciliary nerve to pupillary dilator muscles. Sympathetic fibers also innervate smooth muscle of eyelids (minor retractors) and sweat glands of forehead and face.

Marcus Gunn pupil

Afferent pupillary defect—due to optic nerve damage or severe retinal injury. ↓ bilateral pupillary constriction when light is shone in affected eye relative to unaffected eye. Tested with "swinging flashlight test."

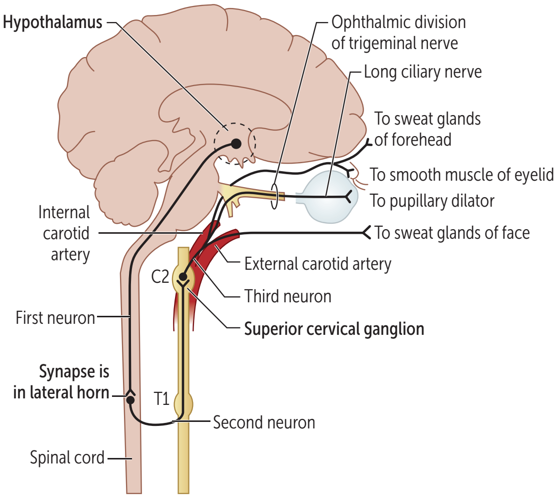
Horner syndrome

Sympathetic denervation of face →:
- **P**tosis (slight drooping of eyelid: superior tarsal muscle)
- **A**nhidrosis (absence of sweating) and flushing of affected side of face
- **M**iosis (pupil constriction)

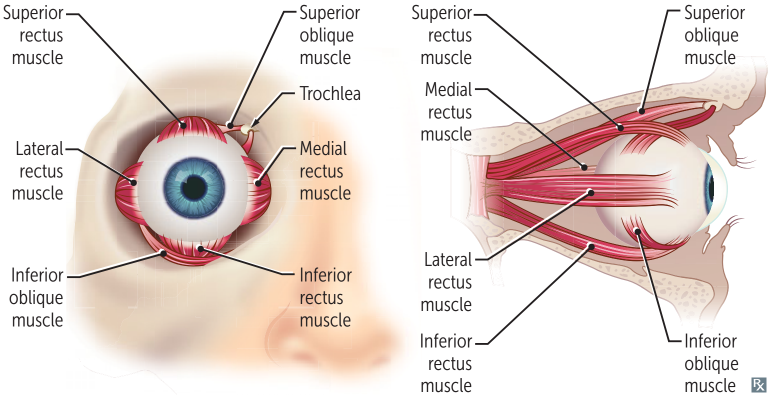
Associated with lesion of spinal cord above T1 (eg, Brown-Séquard syndrome, late-stage syringomyelia) or of the stellate ganglion alongside the spinal cord (eg, Pancoast tumor).

Any interruption results in Horner syndrome.

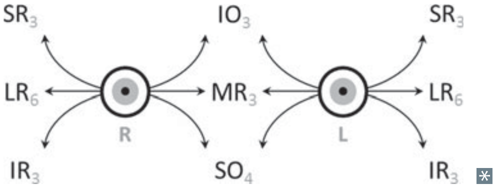
PAM is **horny** (Horner).
Ptosis, **anhidrosis**, and **miosis**.


Hypothalamus
Ophthalmic division of trigeminal nerve
Long ciliary nerve
To sweat glands of forehead
To smooth muscle of eyelid
To pupillary dilator
Internal carotid artery
To sweat glands of face
External carotid artery
C2
Third neuron
Superior cervical ganglion
First neuron
Synapse is in lateral horn
T1
Second neuron
Spinal cord

Ocular motility


Superior rectus muscle
Superior oblique muscle
Trochlea
Lateral rectus muscle
Medial rectus muscle
Inferior oblique muscle
Inferior rectus muscle
Superior rectus muscle
Medial rectus muscle
Lateral rectus muscle
Inferior rectus muscle
Superior oblique muscle
Inferior oblique muscle

CN **VI** innervates the **L**ateral **R**ectus.
CN **IV** innervates the **S**uperior **O**blique.
CN **III** innervates the **R**est.
The "chemical formula" **$LR_6SO_4R_3$**.
The superior oblique abducts, intorts, and depresses while adducted.

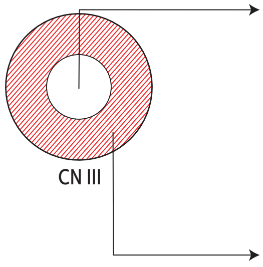

SR_3
IO_3
SR_3
LR_6
MR_3
LR_6
R
L
IR_3
SO_4
IR_3

To test each muscle, ask patient to move his/her eye in the path diagrammed to the right, from neutral position toward the muscle being tested.

Obliques go **O**pposite (left SO and IO tested with patient looking right).
IOU: **IO** tested looking **U**p.

CN III, IV, VI palsies

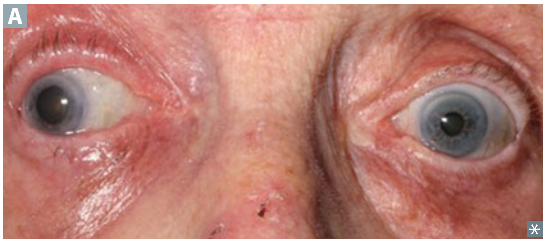
CN III damage



CN III has both motor (central) and parasympathetic (peripheral) components.

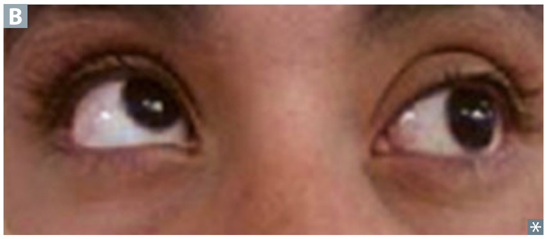
Motor output to extraocular muscles—affected primarily by vascular disease (eg, diabetes mellitus: glucose → sorbitol) due to ↓ diffusion of oxygen and nutrients to the interior fibers from compromised vasculature that resides on outside of nerve. Signs: ptosis, "down and out" gaze.

Parasympathetic output—fibers on the periphery are first affected by compression (eg, PCom aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, "blown pupil" often with "down-and-out" gaze A.



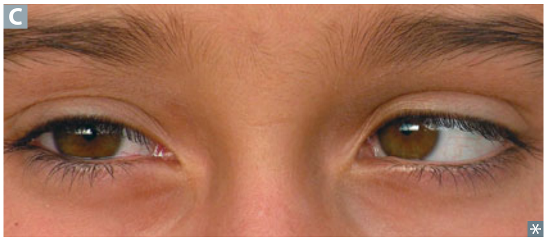
CN IV damage

Eye moves upward, particularly with contralateral gaze B (problems going down stairs, may present with compensatory head tilt in the opposite direction).



CN VI damage

Medially directed eye that cannot abduct C.

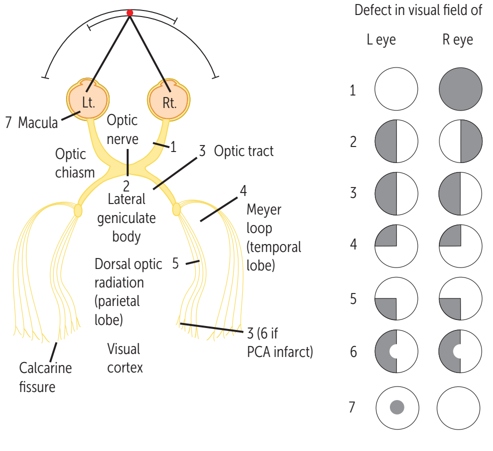


Visual field defects

1. Right anopia
2. Bitemporal hemianopia (pituitary lesion, chiasm)
3. Left homonymous hemianopia
4. Left upper quadrantanopia (right temporal lesion, MCA)
5. Left lower quadrantanopia (right parietal lesion, MCA)
6. Left hemianopia with macular sparing (PCA infarct)
7. Central scotoma (eg, macular degeneration)

Meyer Loop—Lower retina; Loops around inferior horn of Lateral ventricle.

Dorsal optic radiation—superior retina; takes shortest path via internal capsule.


Lt.
Rt.
7 Macula
Optic nerve
1
Optic chiasm
3 Optic tract
2
Lateral geniculate body
4
Meyer loop (temporal lobe)
Dorsal optic radiation (parietal lobe)
5
3 (6 if PCA infarct)
Calcarine fissure
Visual cortex
Defect in visual field of
L eye
R eye
1
2
3
4
5
6
7

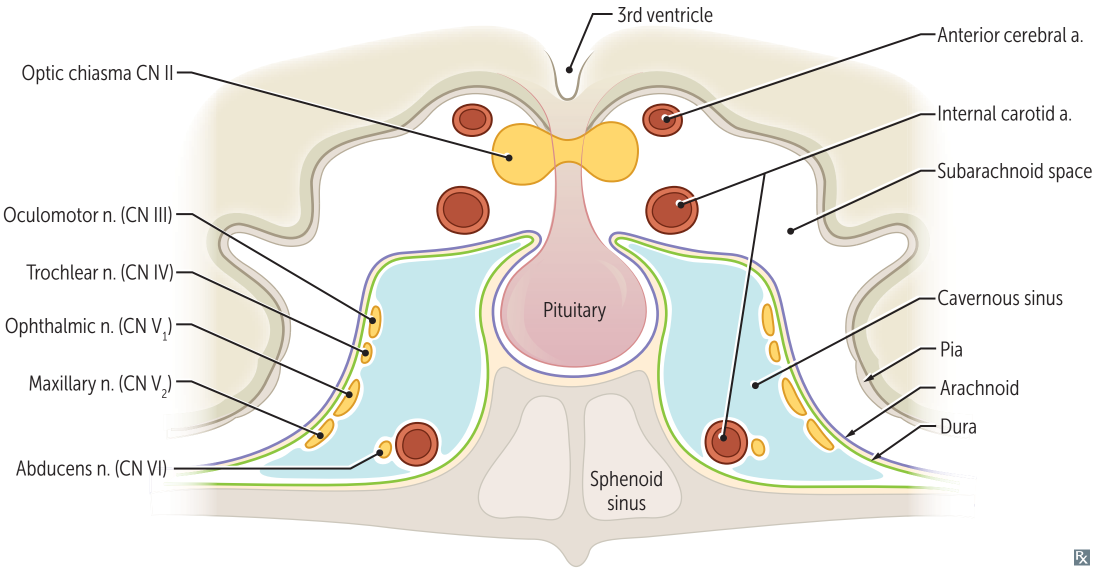
Note: When an image hits 1° visual cortex, it is upside down and left-right reversed.

Cavernous sinus

Collection of venous sinuses on either side of pituitary. Blood from eye and superficial cortex → cavernous sinus → internal jugular vein.

CNs III, IV, V_1, VI, and occasionally V_2 plus postganglionic sympathetic pupillary fibers en route to orbit all pass through cavernous sinus. Cavernous portion of internal carotid artery is also here.

Cavernous sinus syndrome—presents with variable ophthalmoplegia, ↓ corneal sensation, Horner syndrome and occasional decreased maxillary sensation. 2° to pituitary tumor mass effect, carotid-cavernous fistula, or cavernous sinus thrombosis related to infection. CN VI is most susceptible to injury.


3rd ventricle
Anterior cerebral a.
Optic chiasma CN II
Internal carotid a.
Subarachnoid space
Oculomotor n. (CN III)
Trochlear n. (CN IV)
Ophthalmic n. (CN V_1)
Pituitary
Cavernous sinus
Pia
Maxillary n. (CN V_2)
Arachnoid
Dura
Abducens n. (CN VI)
Sphenoid sinus

Internuclear ophthalmoplegia

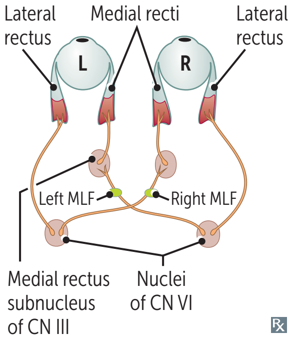
Medial longitudinal fasciculus (MLF): pair of tracts that allows for crosstalk between CN VI and CN III nuclei. Coordinates both eyes to move in same horizontal direction. Highly myelinated (must communicate quickly so eyes move at same time). Lesions may be unilateral or bilateral (latter classically seen in multiple sclerosis).

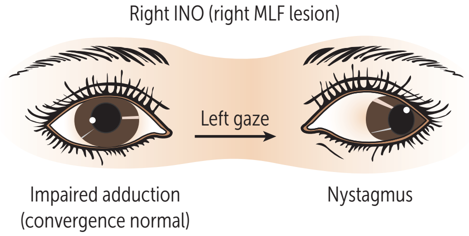
Lesion in MLF = internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy. Lack of communication such that when CN VI nucleus activates ipsilateral lateral rectus, contralateral CN III nucleus does not stimulate medial rectus to contract. Abducting eye gets nystagmus (CN VI overfires to stimulate CN III). Convergence normal.

MLF in **M**S.

When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus.

Directional term (eg, right INO, left INO) refers to which eye is paralyzed.


Lateral rectus
Medial recti
Lateral rectus
L
R
Left MLF
Right MLF
Medial rectus subnucleus of CN III
Nuclei of CN VI


Right INO (right MLF lesion)
Left gaze
Impaired adduction (convergence normal)
Nystagmus

▸ NEUROLOGY—PHARMACOLOGY

Epilepsy drugs

		GENERALIZED					
	PARTIAL (FOCAL)	TONIC-CLONIC	ABSENCE	STATUS EPILEPTICUS	MECHANISM	SIDE EFFECTS	NOTES
Ethosuximide			✓*		Blocks thalamic T-type Ca^{2+} channels	EFGHIJ—Ethosuximide causes Fatigue, GI distress, Headache, Itching (and urticaria), and Stevens-Johnson syndrome	Sucks to have Silent (absence) Seizures
Benzodiazepines (eg, diazepam, lorazepam, midazolam)				✓**	↑ $GABA_A$ action	Sedation, tolerance, dependence, respiratory depression	Also for eclampsia seizures (1st line is $MgSO_4$)
Phenobarbital	✓	✓			↑ $GABA_A$ action	Sedation, tolerance, dependence, induction of cytochrome P-450, cardiorespiratory depression	1st line in neonates
Phenytoin, fosphenytoin	✓	✓*		✓***	Blocks Na^+ channels; zero-order kinetics	Neurologic: nystagmus, diplopia, ataxia, sedation, peripheral neuropathy. Dermatologic: hirsutism, Stevens-Johnson syndrome, gingival hyperplasia, DRESS syndrome. Musculoskeletal: osteopenia, SLE-like syndrome. Hematologic: megaloblastic anemia. Reproductive: teratogenesis (fetal hydantoin syndrome). Other: cytochrome P-450 induction	
Carbamazepine	✓*	✓			Blocks Na^+ channels	Diplopia, ataxia, blood dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis, induction of cytochrome P-450, SIADH, Stevens-Johnson syndrome	1st line for trigeminal neuralgia
Valproic acid	✓	✓*	✓		↑ Na^+ channel inactivation, ↑ GABA concentration by inhibiting GABA transaminase	GI distress, rare but fatal hepatotoxicity (measure LFTs), pancreatitis, neural tube defects, tremor, weight gain, contraindicated in pregnancy	Also used for myoclonic seizures, bipolar disorder, migraine prophylaxis
Vigabatrin	✓				↑ GABA by irreversibly inhibiting GABA transaminase	Permanent visual loss (black box warning)	
Gabapentin	✓				Primarily inhibits high-voltage-activated Ca^{2+} channels; designed as GABA analog	Sedation, ataxia	Also used for peripheral neuropathy, postherpetic neuralgia
Topiramate	✓	✓			Blocks Na^+ channels, ↑ GABA action	Sedation, mental dulling, kidney stones, weight loss, glaucoma	Also used for migraine prevention
Lamotrigine	✓	✓	✓		Blocks voltage-gated Na^+ channels, inhibits the release of glutamate	Stevens-Johnson syndrome (must be titrated slowly)	
Levetiracetam	✓	✓			Unknown; may modulate GABA and glutamate release	Fatigue, drowsiness, headache, neuropsychiatric symptoms (eg, personality changes)	
Tiagabine	✓				↑ GABA by inhibiting reuptake		

* = 1st line; ** = 1st line for acute; *** = 1st line for prophylaxis.

Barbiturates	Phenobarbital, pentobarbital, thiopental, secobarbital.
MECHANISM	Facilitate $GABA_A$ action by ↑ **duration** of Cl^- channel opening, thus ↓ neuron firing (barbi**durat**es ↑ **durat**ion). Contraindicated in porphyria.
CLINICAL USE	Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental).
ADVERSE EFFECTS	Respiratory and cardiovascular depression (can be fatal); CNS depression (can be exacerbated by alcohol use); dependence; drug interactions (induces cytochrome P-450). Overdose treatment is supportive (assist respiration and maintain BP).

Benzodiazepines	Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.	
MECHANISM	Facilitate $GABA_A$ action by ↑ **frequency** of Cl^- channel opening. ↓ REM sleep. Most have long half-lives and active metabolites (exceptions [**ATOM**]: **A**lprazolam, **T**riazolam, **O**xazepam, and **M**idazolam are short acting → higher addictive potential).	“**Fre**nzodiazepines” ↑ **fre**quency. Benzos, barbs, and alcohol all bind the $GABA_A$ receptor, which is a ligand-gated Cl^- channel. **O**xazepam, **T**emazepam, and **L**orazepam are metabolized **O**utside **T**he **L**iver
CLINICAL USE	Anxiety, spasticity, status epilepticus (lorazepam and diazepam), eclampsia, detoxification (especially alcohol withdrawal–DTs), night terrors, sleepwalking, general anesthetic (amnesia, muscle relaxation), hypnotic (insomnia).	
ADVERSE EFFECTS	Dependence, additive CNS depression effects with alcohol. Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA benzodiazepine receptor). Can precipitate seizures by causing acute benzodiazepine withdrawal.	

Nonbenzodiazepine hypnotics	**Z**olpidem, **Z**aleplon, es**Z**opiclone. “All **ZZZ**s put you to sleep.”
MECHANISM	Act via the BZ1 subtype of the GABA receptor. Effects reversed by flumazenil. Sleep cycle less affected as compared with benzodiazepine hypnotics.
CLINICAL USE	Insomnia.
ADVERSE EFFECTS	Ataxia, headaches, confusion. Short duration because of rapid metabolism by liver enzymes. Unlike older sedative-hypnotics, cause only modest day-after psychomotor depression and few amnestic effects. ↓ dependence risk than benzodiazepines.

Suvorexant

MECHANISM	Orexin (hypocretin) receptor antagonist.
CLINICAL USE	Insomnia.
ADVERSE EFFECTS	CNS depression, headache, dizziness, abnormal dreams, upper respiratory tract infection. Contraindicated in patients with narcolepsy. Not recommended in patients with liver disease. No or low physical dependence. Contraindicated with strong CYP3A4 inhibitors.

Ramelteon

MECHANISM	Melatonin receptor agonist, binds MT1 and MT2 in suprachiasmatic nucleus.
CLINICAL USE	Insomnia.
ADVERSE EFFECTS	Dizziness, nausea, fatigue, headache. No dependence (not a controlled substance).

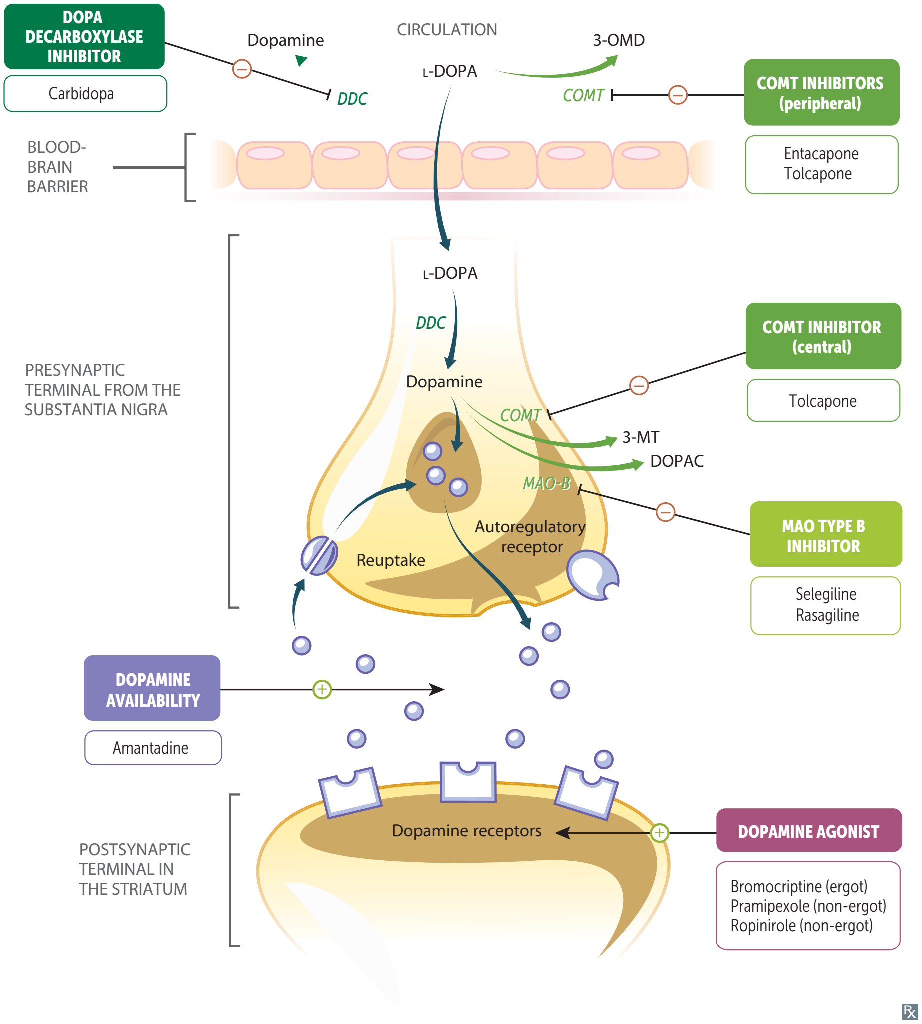
Triptans

	Suma**trip**t**an**	
MECHANISM	5-$\text{HT}_{1B/1D}$ agonists. Inhibit trigeminal nerve activation; prevent vasoactive peptide release; induce vasoconstriction.	A **SUM**o wrestler **TRIP**s **AN**d falls on your **head**.
CLINICAL USE	Acute migraine, cluster **head**ache attacks.	
ADVERSE EFFECTS	Coronary vasospasm (contraindicated in patients with CAD or Prinzmetal angina), mild paresthesia, serotonin syndrome (in combination with other 5-HT agonists).	

Parkinson disease drugs

Parkinsonism is due to loss of dopaminergic neurons and excess cholinergic activity. **B**romocriptine, **A**mantadine, **L**evodopa (with carbidopa), **S**elegiline (and COMT inhibitors), **A**ntimuscarinics (**BALSA**).

STRATEGY	AGENTS
Dopamine agonists	Ergot—**B**romocriptine Non-ergot (preferred)—pramipexole, ropinirole
↑ dopamine availability	**A**mantadine (↑ dopamine release and ↓ dopamine reuptake); toxicity = ataxia, livedo reticularis.
↑ L-DOPA availability	Agents prevent peripheral (pre-BBB) L-DOPA degradation → ↑ L-DOPA entering CNS → ↑ central L-DOPA available for conversion to dopamine. ▪ **L**evodopa (L-DOPA)/carbidopa—carbidopa blocks peripheral conversion of L-DOPA to dopamine by inhibiting DOPA decarboxylase. Also reduces side effects of peripheral L-DOPA conversion into dopamine (eg, nausea, vomiting). ▪ Entacapone, tolcapone—prevent peripheral L-DOPA degradation to 3-O-methyldopa (3-OMD) by inhibiting COMT.
Prevent dopamine breakdown	Agents act centrally (post-BBB) to inhibit breakdown of dopamine. ▪ **S**elegiline—blocks conversion of dopamine into DOPAC by selectively inhibiting MAO-B. ▪ Tolcapone—blocks conversion of dopamine to 3-methoxytyramine (3-MT) by inhibiting central COMT.
Curb excess cholinergic activity	**Benz**tropine, trihexyphenidyl (**A**ntimuscarinic; improves tremor and rigidity but has little effect on bradykinesia in **Park**inson disease). **Park** your Mercedes-**Benz**.


DOPA DECARBOXYLASE INHIBITOR
Carbidopa
Dopamine
CIRCULATION
L-DOPA
3-OMD
DDC
COMT
COMT INHIBITORS (peripheral)
Entacapone
Tolcapone
BLOOD-BRAIN BARRIER
L-DOPA
DDC
Dopamine
PRESYNAPTIC TERMINAL FROM THE SUBSTANTIA NIGRA
COMT INHIBITOR (central)
Tolcapone
COMT
3-MT
DOPAC
MAO-B
Autoregulatory receptor
Reuptake
MAO TYPE B INHIBITOR
Selegiline
Rasagiline
DOPAMINE AVAILABILITY
Amantadine
Dopamine receptors
POSTSYNAPTIC TERMINAL IN THE STRIATUM
DOPAMINE AGONIST
Bromocriptine (ergot)
Pramipexole (non-ergot)
Ropinirole (non-ergot)

Levodopa/carbidopa

MECHANISM	↑ level of dopamine in brain. Unlike dopamine, L-DOPA can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine. Carbidopa, a peripheral DOPA decarboxylase inhibitor, is given with L-DOPA to ↑ the bioavailability of L-DOPA in the brain and to limit peripheral side effects.
CLINICAL USE	Parkinson disease.
ADVERSE EFFECTS	Arrhythmias from ↑ peripheral formation of catecholamines. Long-term use can lead to dyskinesia following administration ("on-off" phenomenon), akinesia between doses.

Selegiline, rasagiline

MECHANISM	Selectively inhibit MAO-B (metabolize dopamine) → ↑ dopamine availability.
CLINICAL USE	Adjunctive agent to L-DOPA in treatment of Parkinson disease.
ADVERSE EFFECTS	May enhance adverse effects of L-DOPA.

Huntington disease drugs

Tetrabenazine and reserpine—inhibit vesicular monoamine transporter (VMAT) → ↓ dopamine vesicle packaging and release.

Haloperidol—D_2 receptor antagonist.

Riluzole

Treatment for ALS that modestly ↑ survival by ↓ glutamate excitotoxicity via an unclear mechanism.

For **Lou** Gehrig disease, give ri**lou**zole.

Alzheimer disease drugs

Memantine

MECHANISM	NMDA receptor antagonist; helps prevent excitotoxicity (mediated by Ca^{2+}).
ADVERSE EFFECTS	Dizziness, confusion, hallucinations.

Donepezil, galantamine, rivastigmine, tacrine

MECHANISM	AChE inhibitors.
ADVERSE EFFECTS	Nausea, dizziness, insomnia.

Anesthetics—general principles

CNS drugs must be lipid soluble (cross the blood-brain barrier) or be actively transported.

Drugs with ↓ solubility in blood = rapid induction and recovery times.

Drugs with ↑ solubility in lipids = ↑ potency = $\frac{1}{\text{MAC}}$

MAC = **M**inimal **A**lveolar **C**oncentration (of inhaled anesthetic) required to prevent 50% of subjects from moving in response to noxious stimulus (eg, skin incision).

Examples: nitrous oxide (N_2O) has ↓ blood and lipid solubility, and thus fast induction and low potency. Halothane, in contrast, has ↑ lipid and blood solubility, and thus high potency and slow induction.

Inhaled anesthetics	Desfl**urane**, haloth**ane**, enfl**urane**, isofl**urane**, sevofl**urane**, methoxyfl**urane**, N_2O.
MECHANISM	Mechanism unknown.
EFFECTS	Myocardial depression, respiratory depression, nausea/emesis, ↑ cerebral blood flow (↓ cerebral metabolic demand).
ADVERSE EFFECTS	**H**epatotoxicity (**h**alothane), **nephr**otoxicity (**meth**oxyflurane), proconvulsant (**e**nflurane, **e**pileptogenic), expansio**n** of trapped gas in a body cavity (**N**$_2$O). Malignant hyperthermia—rare, life-threatening condition in which inhaled anesthetics or succinylcholine induce fever and severe muscle contractions. Susceptibility is often inherited as autosomal dominant with variable penetrance. Mutations in voltage-sensitive ryanodine receptor cause ↑ Ca^{2+} release from sarcoplasmic reticulum. Treatment: dantrolene (a ryanodine receptor antagonist).

Intravenous anesthetics	**Th**e **Mi**ghty **K**ing **Propo**ses to **Op**rah.
Barbiturates (Thiopental)	High potency, high lipid solubility, rapid entry into brain. Used for induction of anesthesia and short surgical procedures. Effect terminated by rapid redistribution into tissue and fat. ↓ cerebral blood flow.
Benzodiazepines (Midazolam)	Used for endoscopy; used adjunctively with gaseous anesthetics and narcotics. May cause severe postoperative respiratory depression, ↓ BP (treat overdose with flumazenil), anterograde amnesia.
Arylcyclohexylamines (Ketamine)	PCP analogs that act as dissociative anesthetics. Block NMDA receptors. Cardiovascular stimulants. Cause disorientation, hallucination, unpleasant dreams. ↑ cerebral blood flow.
Propofol	Used for sedation in ICU, rapid anesthesia induction, short procedures. Less postoperative nausea than thiopental. Potentiates $GABA_A$.
Opioids	Morphine, fentanyl used with other CNS depressants during general anesthesia.

Local anesthetics	Esters—procaine, cocaine, tetracaine, benzocaine. Amides—l**I**doca**I**ne, mep**I**vaca**I**ne, bup**I**vaca**I**ne (am**I**des have **2 I**'s in name).
MECHANISM	Block Na^+ channels by binding to specific receptors on inner portion of channel. Most effective in rapidly firing neurons. 3° amine local anesthetics penetrate membrane in uncharged form, then bind to ion channels as charged form. Can be given with vasoconstrictors (usually epinephrine) to enhance local action—↓ bleeding, ↑ anesthesia by ↓ systemic concentration. In infected (acidic) tissue, alkaline anesthetics are charged and cannot penetrate membrane effectively → need more anesthetic. Order of nerve blockade: small-diameter fibers > large diameter. Myelinated fibers > unmyelinated fibers. Overall, size factor predominates over myelination such that small myelinated fibers > small unmyelinated fibers > large myelinated fibers > large unmyelinated fibers. Order of loss: (1) pain, (2) temperature, (3) touch, (4) pressure.
CLINICAL USE	Minor surgical procedures, spinal anesthesia. If allergic to esters, give amides.
ADVERSE EFFECTS	CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, arrhythmias (cocaine), methemoglobinemia (benzocaine).

Neuromuscular blocking drugs	Muscle paralysis in surgery or mechanical ventilation. Selective for Nm nicotinic receptors at neuromuscular junction but not autonomic Nn receptors.
Depolarizing	Succinylcholine—strong ACh receptor agonist; produces sustained depolarization and prevents muscle contraction. Reversal of blockade: ▪ Phase I (prolonged depolarization)—no antidote. Block potentiated by cholinesterase inhibitors. ▪ Phase II (repolarized but blocked; ACh receptors are available, but desensitized)—may be reversed with cholinesterase inhibitors. Complications include hypercalcemia, hyperkalemia, malignant hyperthermia.
Nondepolarizing	Tubo**cur**arine, atra**cur**ium, miva**cur**ium, pan**cur**onium, ve**cur**onium, ro**cur**onium—competitive antagonists—compete with ACh for receptors. Reversal of blockade—neostigmine (must be given with atropine to prevent muscarinic effects such as bradycardia), edrophonium, and other cholinesterase inhibitors.

Dantrolene

MECHANISM	Prevents release of Ca^{2+} from the sarcoplasmic reticulum of skeletal muscle by binding to the ryanodine receptor.
CLINICAL USE	Malignant hyperthermia and neuroleptic malignant syndrome (a toxicity of antipsychotic drugs).

Baclofen

MECHANISM	Activates $GABA_B$ receptors at spinal cord level, inducing skeletal muscle relaxation.
CLINICAL USE	Muscle spasms (eg, acute low back pain), multiple sclerosis.

Cyclobenzaprine

MECHANISM	Centrally acting skeletal muscle relaxant. Structurally related to TCAs, similar anticholinergic side effects.
CLINICAL USE	Muscle spasms.

Opioid analgesics	Morphine, oxycodone, fentanyl, codeine, loperamide, methadone, meperidine, dextromethorphan, diphenoxylate, pentazocine.
MECHANISM	Act as agonists at opioid receptors (μ = β-endorphin, δ = enkephalin, κ = dynorphin) to modulate synaptic transmission—open K^+ channels, close Ca^{2+} channels → ↓ synaptic transmission. Inhibit release of ACh, norepinephrine, 5-HT, glutamate, substance P.
CLINICAL USE	Pain, cough suppression (dextromethorphan), diarrhea (loperamide, diphenoxylate), acute pulmonary edema, maintenance programs for heroin addicts (methadone, buprenorphine + naloxone).
ADVERSE EFFECTS	Nausea, vomiting, pruritus, addiction, respiratory depression, constipation, miosis (except meperidine → mydriasis), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Toxicity treated with naloxone (opioid receptor antagonist) and relapse prevention with naltrexone once detoxified.

Pentazocine

MECHANISM	κ-opioid receptor agonist and μ-opioid receptor weak antagonist or partial agonist.
CLINICAL USE	Analgesia for moderate to severe pain.
ADVERSE EFFECTS	Can cause opioid withdrawal symptoms if patient is also taking full opioid antagonist (competition for opioid receptors).

Butorphanol

MECHANISM	κ-opioid receptor agonist and μ-opioid receptor partial agonist; produces analgesia.
CLINICAL USE	Severe pain (eg, migraine, labor). Causes less respiratory depression than full opioid agonists.
ADVERSE EFFECTS	Can cause opioid withdrawal symptoms if patient is also taking full opioid agonist (competition for opioid receptors). Overdose not easily reversed with naloxone.

Tramadol

MECHANISM	Very weak opioid agonist; also inhibits 5-HT and norepinephrine reuptake (works on multiple neurotransmitters—"**tram it all**" in with **tramadol**).
CLINICAL USE	Chronic pain.
ADVERSE EFFECTS	Similar to opioids. Decreases seizure threshold. Serotonin syndrome.

Glaucoma drugs

↓ IOP via ↓ amount of aqueous humor (inhibit synthesis/secretion or ↑ drainage).

DRUG	MECHANISM	ADVERSE EFFECTS
α-agonists		
Epinephrine (α_1), brimonidine (α_2)	↓ aqueous humor synthesis via vasoconstriction (epinephrine) ↓ aqueous humor synthesis (brimonidine)	Mydriasis (α_1); do not use in closed-angle glaucoma Blurry vision, ocular hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus
β-blockers		
Timolol, betaxolol, carteolol	↓ aqueous humor synthesis	No pupillary or vision changes
Diuretics		
Acetazolamide	↓ aqueous humor synthesis via inhibition of carbonic anhydrase	No pupillary or vision changes
Cholinomimetics (M_3)		
Direct (pilocarpine, carbachol) **Indirect (physostigmine, echothiophate)**	↑ outflow of aqueous humor via contraction of ciliary muscle and opening of trabecular meshwork Use pilocarpine in emergencies—very effective at opening meshwork into canal of Schlemm	Miosis (contraction of pupillary sphincter muscles) and cyclospasm (contraction of ciliary muscle)
Prostaglandin		
Bimatoprost, latanoprost ($PGF_{2\alpha}$)	↑ outflow of aqueous humor via ↓ resistance of flow through uveoscleral pathway	Darkens color of iris (browning), eyelash growth

NOTES

HIGH-YIELD PRINCIPLES IN

Psychiatry

“Words of comfort, skillfully administered, are the oldest therapy known to man.”

—Louis Nizer

“All men should strive to learn before they die what they are running from, and to, and why.”

—James Thurber

“Man wishes to be happy even when he so lives as to make happiness impossible.”

—St. Augustine

“It is far more important to know what sort of person has a disease, than to know what sort of disease a person has.”

—Hippocrates

▸ Psychology 524

▸ Pathology 526

▸ Pharmacology 542

▶ PSYCHIATRY—PSYCHOLOGY

Classical conditioning	Learning in which a natural response (salivation) is elicited by a conditioned, or learned, stimulus (bell) that previously was presented in conjunction with an unconditioned stimulus (food).	Usually deals with **involuntary** responses. Pavlov's classical experiments with dogs—ringing the bell provoked salivation.

Operant conditioning	Learning in which a particular action is elicited because it produces a punishment or reward. Usually deals with **voluntary** responses.
Reinforcement	Target behavior (response) is followed by desired reward (positive reinforcement) or removal of aversive stimulus (negative reinforcement).
Extinction	Discontinuation of reinforcement (positive or negative) eventually eliminates behavior. Can occur in operant or classical conditioning.
Punishment	Repeated application of aversive stimulus (positive punishment) or removal of desired reward (negative punishment) to extinguish unwanted behavior (Skinner's operant conditioning quadrant).

	Increase behavior	Decrease behavior
Add a stimulus	Positive reinforcement	Positive punishment
Remove a stimulus	Negative reinforcement	Negative punishment

Transference and countertransference

Transference	Patient projects feelings about formative or other important persons onto physician (eg, psychiatrist is seen as parent).
Countertransference	Doctor projects feelings about formative or other important persons onto patient (eg, patient reminds physician of younger sibling).

Ego defenses	Mental processes (unconscious or conscious) used to resolve conflict and prevent undesirable feelings (eg, anxiety, depression).

IMMATURE DEFENSES	DESCRIPTION	EXAMPLE
Acting out	Expressing unacceptable feelings and thoughts through actions.	Tantrums.
Denial	Avoiding the awareness of some painful reality.	A patient with cancer plans a full-time work schedule despite being warned of significant fatigue during chemotherapy.
Displacement	Redirection of emotions or impulses to a neutral person or object (vs projection).	A teacher is yelled at by the principal. Instead of confronting the principal directly, the teacher goes home and criticizes her husband's dinner selection.
Dissociation	Temporary, drastic change in personality, memory, consciousness, or motor behavior to avoid emotional stress. Patient has incomplete or no memory of traumatic event.	A victim of sexual abuse suddenly appears numb and detached when she is exposed to her abuser.

Ego defenses *(continued)*

IMMATURE DEFENSES	DESCRIPTION	EXAMPLE
Fixation	Partially remaining at a more childish level of development (vs regression).	A surgeon throws a tantrum in the operating room because the last case ran very late.
Idealization	Expressing extremely positive thoughts of self and others while ignoring negative thoughts.	A patient boasts about his physician and his accomplishments while ignoring any flaws.
Identification	Largely unconscious assumption of the characteristics, qualities, or traits of another person or group.	A resident starts putting his stethoscope in his pocket like his favorite attending, instead of wearing it around his neck like before.
Intellectualization	Using facts and logic to emotionally distance oneself from a stressful situation.	In a therapy session, patient diagnosed with cancer focuses only on rates of survival.
Isolation (of affect)	Separating feelings from ideas and events.	Describing murder in graphic detail with no emotional response.
Passive aggression	Demonstrating hostile feelings in a nonconfrontational manner; showing indirect opposition.	Disgruntled employee is repeatedly late to work, but won't admit it is a way to get back at the manager.
Projection	Attributing an unacceptable internal impulse to an external source (vs displacement).	A man who wants to cheat on his wife accuses his wife of being unfaithful.
Rationalization	Proclaiming logical reasons for actions actually performed for other reasons, usually to avoid self-blame.	After getting fired, claiming that the job was not important anyway.
Reaction formation	Replacing a warded-off idea or feeling by an (unconsciously derived) emphasis on its opposite (vs sublimation).	A patient with libidinous thoughts enters a monastery.
Regression	**Involuntarily** turning back the maturational clock and going back to earlier modes of dealing with the world (vs fixation).	Seen in children under stress such as illness, punishment, or birth of a new sibling (eg, bedwetting in a previously toilet-trained child when hospitalized).
Repression	Involuntarily withholding an idea or feeling from conscious awareness (vs suppression).	A 20-year-old does not remember going to counseling during his parents' divorce 10 years earlier.
Splitting	Believing that people are either all good or all bad at different times due to intolerance of ambiguity. Commonly seen in borderline personality disorder.	A patient says that all the nurses are cold and insensitive but that the doctors are warm and friendly.
MATURE DEFENSES		
Sublimation	Replacing an unacceptable wish with a course of action that is similar to the wish but does not conflict with one's value system (vs reaction formation).	Teenager's aggression toward his father is redirected to perform well in sports.
Altruism	Alleviating negative feelings via unsolicited generosity.	Mafia boss makes large donation to charity.
Suppression	**Intentionally** withholding an idea or feeling from conscious awareness (vs repression); temporary.	Choosing to not worry about the big game until it is time to play.
Humor	Appreciating the amusing nature of an anxiety-provoking or adverse situation.	Nervous medical student jokes about the boards.
	Mature adults wear a SASH.	

▶ PSYCHIATRY—PATHOLOGY

Infant deprivation effects

Long-term deprivation of affection results in:
- Failure to thrive
- Poor language/socialization skills
- Lack of basic trust
- Reactive attachment disorder (infant withdrawn/unresponsive to comfort)

Deprivation for > 6 months can lead to irreversible changes.

Severe deprivation can result in infant death.

Child abuse

	Physical abuse	Sexual abuse
EVIDENCE	Fractures (eg, ribs, long bone spiral, multiple in different stages of healing), bruises (eg, trunk, ear, neck; in pattern of implement), burns (eg, cigarette, buttocks/thighs), subdural hematomas, retinal hemorrhages. During exam, children often avoid eye contact.	Genital, anal, or oral trauma; STIs; UTIs.
ABUSER	Usually biological mother.	Known to victim, usually male.
EPIDEMIOLOGY	40% of deaths related to child abuse or neglect occur in children < 1 year old.	Peak incidence 9–12 years old.

Child neglect

Failure to provide a child with adequate food, shelter, supervision, education, and/or affection. Most common form of child maltreatment. Evidence: poor hygiene, malnutrition, withdrawal, impaired social/emotional development, failure to thrive.

As with child abuse, suspected child neglect must be reported to local child protective services.

Vulnerable child syndrome

Parents perceive the child as especially susceptible to illness or injury. Usually follows a serious illness or life-threatening event. Can result in missed school or overuse of medical services.

Childhood and early-onset disorders

Attention-deficit hyperactivity disorder	Onset before age 12. Limited attention span and poor impulse control. Characterized by hyperactivity, impulsivity, and/or inattention in multiple settings (school, home, places of worship, etc). Normal intelligence, but commonly coexists with difficulties in school. Continues into adulthood in as many as 50% of individuals. Treatment: stimulants (eg, methylphenidate) +/– cognitive behavioral therapy (CBT); alternatives include atomoxetine, guanfacine, clonidine.
Autism spectrum disorder	Characterized by poor social interactions, social communication deficits, repetitive/ritualized behaviors, restricted interests. Must present in early childhood. May be accompanied by intellectual disability; rarely accompanied by unusual abilities (savants). More common in boys. Associated with ↑ head/brain size.
Rett syndrome	X-linked dominant disorder seen almost exclusively in girls (affected males die in utero or shortly after birth). Majority of cases are caused by de novo mutation of *MECP2*. Symptoms usually become apparent around ages 1–4, including regression characterized by loss of development, loss of verbal abilities, intellectual disability, ataxia, stereotyped hand-wringing. No longer a solitary diagnosis within DSM-5.
Conduct disorder	Repetitive and pervasive behavior violating the basic rights of others or societal norms (eg, aggression to people and animals, destruction of property, theft). After age 18, often reclassified as antisocial personality disorder. Treatment for both: psychotherapy such as CBT.
Oppositional defiant disorder	Enduring pattern of hostile, defiant behavior toward authority figures in the absence of serious violations of social norms. Treatment: psychotherapy such as CBT.
Separation anxiety disorder	Overwhelming fear of separation from home or attachment figure. Can be normal behavior up to age 3–4. May lead to factitious physical complaints to avoid school. Treatment: CBT, play therapy, family therapy.
Tourette syndrome	Onset before age 18. Characterized by sudden, rapid, recurrent, nonrhythmic, stereotyped motor and vocal tics that persist for **> 1 year**. Coprolalia (involuntary obscene speech) found in only 10–20% of patients. Associated with OCD and ADHD. Treatment: psychoeducation, behavioral therapy. For intractable and distressing tics, high-potency antipsychotics (eg, haloperidol, fluphenazine, pimozide), tetrabenazine, α_2-agonists (eg, guanfacine, clonidine), or atypical antipsychotics may be used.
Disruptive mood dysregulation disorder	Onset before age 10. Severe and recurrent temper outbursts out of proportion to situation. Child is constantly angry and irritable between outbursts. Treatment: psychostimulants, antipsychotics, CBT.

Orientation	Patient's ability to know who he or she is, where he or she is, and the date and time. Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies.	Order of loss: time → place → person.

Amnesias

Retrograde amnesia	Inability to remember things that occurred **before** a CNS insult.
Anterograde amnesia	Inability to remember things that occurred **a**fter a CNS insult (↓ acquisition of new memory).
Korsakoff syndrome	Amnesia (anterograde > retrograde) caused by vitamin B_1 deficiency and associated destruction of mammillary bodies. Seen in alcoholics as a late neuropsychiatric manifestation of Wernicke encephalopathy. Confabulations are characteristic.
Dissociative amnesia	Inability to recall important personal information, usually subsequent to severe trauma or stress. May be accompanied by **dissociative fugue** (abrupt travel or wandering during a period of dissociative amnesia, associated with traumatic circumstances).

Dissociative disorders

Dissociative identity disorder	Formerly known as multiple personality disorder. Presence of 2 or more distinct identities or personality states. More common in women. Associated with history of sexual abuse, PTSD, depression, substance abuse, borderline personality, somatoform conditions.
Depersonalization/derealization disorder	Persistent feelings of detachment or estrangement from one's own body, thoughts, perceptions, and actions (depersonalization) or one's environment (derealization).

Delirium	"Waxing and waning" level of consciousness with acute onset; rapid ↓ in attention span and level of arousal. Characterized by disorganized thinking, hallucinations (often visual), illusions, misperceptions, disturbance in sleep-wake cycle, cognitive dysfunction. Usually 2° to other illness (eg, CNS disease, infection, trauma, substance abuse/withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention). Most common presentation of altered mental status in inpatient setting, especially in the intensive care unit and with prolonged hospital stays. Commonly, diffuse slowing EEG. Treatment is aimed at identifying and addressing underlying condition. Antipsychotics may be used acutely as needed.	Deli**rium** = changes in senso**rium**. May be caused by medications (eg, anticholinergics), especially in the elderly. **Reversible**.

Dementia	↓ in intellectual function without affecting level of consciousness. Characterized by memory deficits, apraxia, aphasia, agnosia, loss of abstract thought, behavioral/personality changes, impaired judgment. A patient with dementia can develop delirium (eg, patient with Alzheimer disease who develops pneumonia is at ↑ risk for delirium). Irreversible causes: Alzheimer disease, Lewy body dementia, Huntington disease, Pick disease, cerebral infarct, Wilson disease, Creutzfeldt-Jakob disease, chronic substance abuse (due to neurotoxicity of drugs), HIV. Reversible causes: hypothyroidism, depression, vitamin deficiency (B_1, B_3, B_{12}), normal pressure hydrocephalus, neurosyphilis. ↑ incidence with age. EEG usually normal.	"De**mem**tia" is characterized by **mem**ory loss. Usually **irreversible**. In elderly patients, depression and hypothyroidism may present like dementia (pseudodementia). Screen for depression, exclude neurosyphilis with RPR if high clinical suspicion, and measure TSH, B_{12} levels.

Psychosis	Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thought/speech. Can occur in patients with medical illness, psychiatric illness, or both.
Delusions	Unique, false, fixed, idiosyncratic beliefs that persist despite the facts and are not typical of a patient's culture or religion (eg, thinking aliens are communicating with you). Types include erotomanic, grandiose, jealous, persecutory, somatic, mixed, and unspecified.
Disorganized thought	Speech may be incoherent ("word salad"), tangential, or derailed ("loose associations").
Hallucinations	Perceptions in the absence of external stimuli (eg, seeing a light that is not actually present). Contrast with illusions, misperceptions of real external stimuli. Types include: ▪ Visual—more commonly a feature of medical illness (eg, drug intoxication) than psychiatric illness. ▪ Auditory—more commonly a feature of psychiatric illness (eg, schizophrenia) than medical illness. ▪ Olfactory—often occur as an aura of temporal lobe epilepsy (eg, burning rubber) and in brain tumors. ▪ Gustatory—rare, but seen in epilepsy. ▪ Tactile—common in alcohol withdrawal and stimulant use (eg, cocaine, amphetamines), delusional parasitosis, "cocaine crawlies." ▪ Hypna**go**gic—occurs while **go**ing to sleep. Sometimes seen in narcolepsy. ▪ Hypno**pomp**ic—occurs while waking from sleep ("**pomp**ous upon awakening"). Sometimes seen in narcolepsy.

Schizophrenia

Chronic mental disorder with periods of psychosis, disturbed behavior and thought, and decline in functioning **lasting > 6 months**. Associated with ↑ dopaminergic activity, ↓ dendritic branching.

Diagnosis requires at least 2 of the following, and at least 1 of these should include 1–3 (first 4 are "positive symptoms"):

1. Delusions
2. Hallucinations—often auditory
3. Disorganized speech
4. Disorganized or catatonic behavior
5. Negative symptoms (affective flattening, avolition, anhedonia, asociality, alogia)

Brief psychotic disorder—**lasting < 1 month**, usually stress related.

Schizophreniform disorder—**lasting 1–6 months**.

Schizoaffective disorder—Meets criteria for schizophrenia in addition to major mood disorder (major depressive or bipolar). To differentiate from a major mood disorder with psychotic features, patient must have **> 2 weeks** of hallucinations or delusions without major mood episode.

Frequent cannabis use is associated with psychosis/schizophrenia in teens.

Lifetime prevalence—1.5% (males = females, African Americans = Caucasians). Presents earlier in men (late teens to early 20s vs late 20s to early 30s in women). Patients are at ↑ risk for suicide.

Ventriculomegaly on brain imaging.

Treatment: atypical antipsychotics (eg, risperidone) are first line.

Negative symptoms often persist after treatment, despite resolution of positive symptoms.

Delusional disorder

Fixed, persistent, false belief system **lasting > 1 month**. Functioning otherwise not impaired (eg, a woman who genuinely believes she is married to a celebrity when, in fact, she is not). Can be shared by individuals in close relationships (folie à deux).

Mood disorder

Characterized by an abnormal range of moods or internal emotional states and loss of control over them. Severity of moods causes distress and impairment in social and occupational functioning. Includes major depressive disorder, bipolar disorder, dysthymic disorder, and cyclothymic disorder. Episodic superimposed psychotic features (delusions or hallucinations) may be present.

Manic episode

Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently ↑ activity or energy **lasting at least 1 week**. Often disturbing to patient.

Diagnosis requires hospitalization or at least 3 of the following (manics **DIG FAST**):

- Distractibility
- Irresponsibility—seeks pleasure without regard to consequences (hedonistic)
- Grandiosity—inflated self-esteem
- Flight of ideas—racing thoughts
- ↑ in goal-directed Activity/psychomotor Agitation
- ↓ need for Sleep
- Talkativeness or pressured speech

Hypomanic episode	Like a manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization. No psychotic features. **Lasts at least 4 consecutive days**.
Bipolar disorder (manic depression)	Bipolar I defined by presence of at least 1 manic episode +/– a hypomanic or depressive episode. Bipolar II defined by presence of a hypomanic and a depressive episode. Patient's mood and functioning usually return to normal between episodes. Use of antidepressants can precipitate mania. High suicide risk. Treatment: mood stabilizers (eg, lithium, valproic acid, carbamazepine, lamotrigine), atypical antipsychotics. **Cyclothymic disorder**—milder form of bipolar disorder **lasting at least 2 years**, fluctuating between mild depressive and hypomanic symptoms.
Major depressive disorder	Episodes characterized by at least 5 of the 9 diagnostic symptoms **lasting ≥ 2 weeks** (symptoms must include patient-reported depressed mood or anhedonia). Treatment: CBT and SSRIs are first line. SNRIs, mirtazapine, bupropion can also be considered. Antidepressants are indicated if bipolar disorder is ruled out. Electroconvulsive therapy (ECT) in select patients. **Persistent depressive disorder (dysthymia)**—depression, often milder, **lasting at least 2 years**. Diagnostic symptoms: SIG E CAPS: ▪ Depressed mood ▪ Sleep disturbance ▪ Loss of Interest (anhedonia) ▪ Guilt or feelings of worthlessness ▪ Energy loss and fatigue ▪ Concentration problems ▪ Appetite/weight changes ▪ Psychomotor retardation or agitation ▪ Suicidal ideations Patients with depression typically have the following changes in their sleep stages: ▪ ↓ slow-wave sleep ▪ ↓ REM latency ▪ ↑ REM early in sleep cycle ▪ ↑ total REM sleep ▪ Repeated nighttime awakenings ▪ Early-morning awakening (terminal insomnia)
Depression with atypical features	Characterized by mood reactivity (being able to experience improved mood in response to positive events, albeit briefly), "reversed" vegetative symptoms (hypersomnia, hyperphagia), leaden paralysis (heavy feeling in arms and legs), long-standing interpersonal rejection sensitivity. Most common subtype of depression. Treatment: CBT and SSRIs are first line. MAO inhibitors are effective but not first line because of their risk profile.

Postpartum mood disturbances

Onset within 4 weeks of delivery.

Maternal (postpartum) "blues"

50–85% incidence rate. Characterized by depressed affect, tearfulness, and fatigue starting 2–3 days after delivery. Usually resolves within 10 days. Treatment: supportive. Follow up to assess for possible postpartum depression.

Postpartum depression

10–15% incidence rate. Characterized by depressed affect, anxiety, and poor concentration for ≥ 2 weeks. Treatment: CBT and SSRIs are first line.

Postpartum psychosis

0.1–0.2% incidence rate. Characterized by mood-congruent delusions, hallucinations, and thoughts of harming the baby or self. Risk factors include history of bipolar or psychotic disorder, first pregnancy, family history, recent discontinuation of psychotropic medication. Treatment: hospitalization and initiation of atypical antipsychotic; if insufficient, ECT may be used.

Grief

The five stages of grief per the Kübler-Ross model are denial, anger, bargaining, depression, and acceptance, not necessarily in that order. Other normal grief symptoms include shock, guilt, sadness, anxiety, yearning, and somatic symptoms. Simple hallucinations of the deceased person are common (eg, hearing the deceased speaking). Duration varies widely; usually **< 6 months.**

Pathologic grief is persistent and causes functional impairment. Can meet criteria for major depressive episode.

Electroconvulsive therapy

Used mainly for treatment-refractory depression, depression with psychotic symptoms, and acutely suicidality. Produces grand mal seizure in an anesthetized patient. Adverse effects include disorientation, temporary headache, partial anterograde/retrograde amnesia usually resolving in 6 months. Safe in pregnancy.

Risk factors for suicide completion

Sex (male)
Age (young adult or elderly)
Depression
Previous attempt (highest risk factor)
Ethanol or drug use
Rational thinking loss (psychosis)
Sickness (medical illness)
Organized plan
No spouse or other social support
Stated future intent

SAD PERSONS are more likely to complete suicide.

Most common method in US is firearms; access to guns ↑ risk of suicide completion.

Women try more often; men complete more often.

Anxiety disorder

Inappropriate experience of fear/worry and its physical manifestations (anxiety) incongruent with the magnitude of the perceived stressor. Symptoms interfere with daily functioning and are not attributable to another mental disorder, medical condition, or substance abuse. Includes panic disorder, phobias, generalized anxiety disorder, and selective mutism. Treatment: CBT, SSRIs, SNRIs.

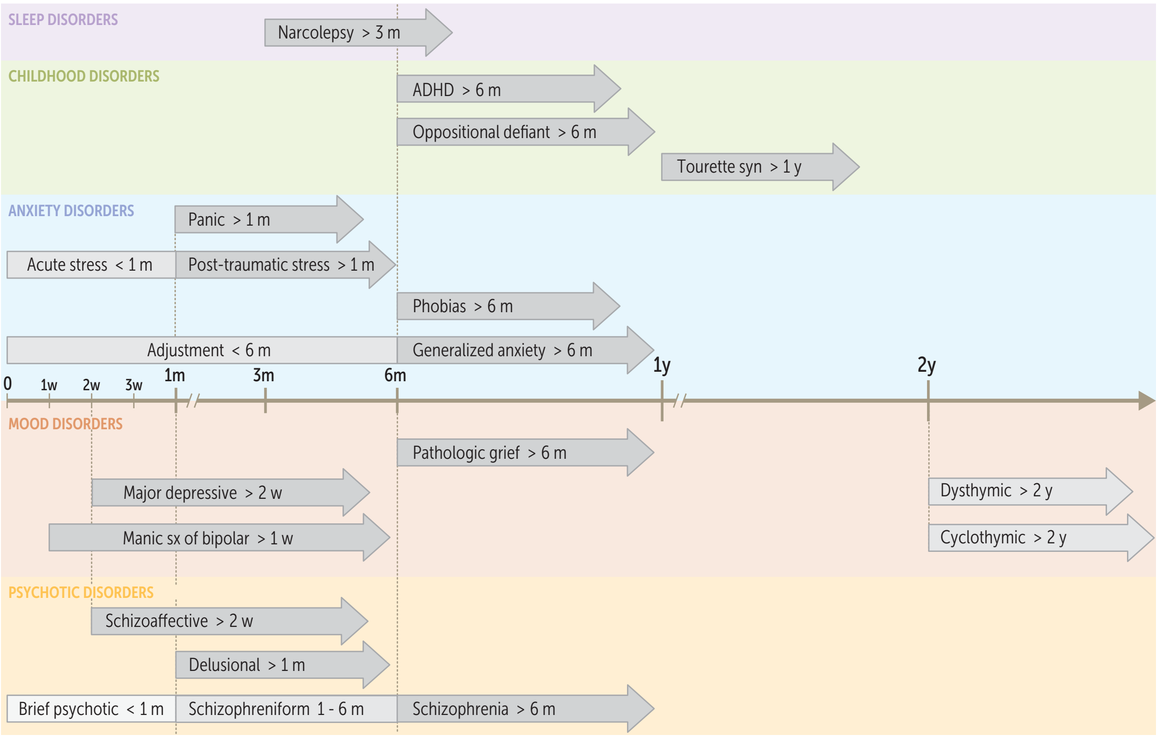
Panic disorder	Defined by recurrent panic attacks (periods of intense fear and discomfort peaking in 10 minutes with at least 4 of the following): **P**alpitations, **P**aresthesias, de**P**ersonalization or derealization, **A**bdominal distress or **N**ausea, **I**ntense fear of dying, **I**ntense fear of losing control or "going crazy," l**I**ght-headedness, **C**hest pain, **C**hills, **C**hoking, **S**weating, **S**haking, **S**hortness of breath. Strong genetic component. ↑ risk of suicide. Treatment: CBT, SSRIs, and venlafaxine are first line. Benzodiazepines occasionally used in acute setting.	**PANICS**. Diagnosis requires attack followed by 1 month (or more) of 1 (or more) of the following: ▪ Persistent concern of additional attacks ▪ Worrying about consequences of attack ▪ Behavioral change related to attacks Symptoms are the systemic manifestations of fear.
Specific phobia	Severe, persistent (**≥ 6 months**) fear or anxiety due to presence or anticipation of a specific object or situation. Person often recognizes fear is excessive. Can be treated with systematic desensitization. **Social anxiety disorder**—exaggerated fear of embarrassment in social situations (eg, public speaking, using public restrooms). Treatment: CBT, SSRIs, venlafaxine. For only occasional anxiety-inducing situations, benzodiazepine or β-blocker. **Agoraphobia**—irrational fear/anxiety while facing or anticipating ≥ 2 specific situations (eg, open/closed spaces, lines, crowds, public transport). If severe, patients may refuse to leave their homes. Associated with panic disorder. Treatment: CBT, SSRIs.	
Generalized anxiety disorder	Anxiety **lasting > 6 months** unrelated to a specific person, situation, or event. Associated with restlessness, irritability, sleep disturbance, fatigue, muscle tension, difficulty concentrating. Treatment: CBT, SSRIs, SNRIs are first line. Buspirone, TCAs, benzodiazepines are second line. **Adjustment disorder**—emotional symptoms (anxiety, depression) that occur within 3 months of an identifiable psychosocial stressor (eg, divorce, illness) **lasting < 6 months** once the stressor has ended. If stressor lasts > 6 months and causes continual impairment, it is GAD. Treatment: CBT, SSRIs.	
Obsessive-compulsive disorder	Recurring intrusive thoughts, feelings, or sensations (obsessions) that cause severe distress; relieved in part by the performance of repetitive actions (compulsions). Ego-dystonic: behavior inconsistent with one's own beliefs and attitudes (vs obsessive-compulsive personality disorder). Associated with Tourette syndrome. Treatment: CBT, SSRIs, and clomipramine are first line. **Body dysmorphic disorder**—preoccupation with minor or imagined defect in appearance → significant emotional distress or impaired functioning; patients often repeatedly seek cosmetic treatment. Treatment: CBT.	

Post-traumatic stress disorder

Exposure to prior trauma (eg, witnessing death, experiencing serious injury or rape) → persistent **H**yperarousal, **A**voidance of associated stimuli, intrusive **R**eexperiencing of the event (nightmares, flashbacks), changes in cognition or mood (fear, horror, **D**istress) (having PTSD is **HARD**). Disturbance **lasts > 1 month** with significant distress or impaired social-occupational functioning. Treatment: CBT, SSRIs, and venlafaxine are first line. Prazosin can reduce nightmares.

Acute stress disorder—lasts between 3 days and 1 month. Treatment: CBT; pharmacotherapy is usually not indicated.

Diagnostic criteria by symptom duration



Personality

Personality trait	An enduring, repetitive pattern of perceiving, relating to, and thinking about the environment and oneself.
Personality disorder	Inflexible, maladaptive, and rigidly pervasive pattern of behavior causing subjective distress and/or impaired functioning; person is usually not aware of problem. Usually presents by early adulthood. Three clusters, A, B, and C; remember as **Weird**, **Wild**, and **Worried** based on symptoms.

Cluster A personality disorders	Odd or eccentric; inability to develop meaningful social relationships. No psychosis; genetic association with schizophrenia.	“**Weird.**” Cluster **A**: **A**ccusatory, **A**loof, **A**wkward.
Paranoid	Pervasive distrust (**A**ccusatory) and suspiciousness of others and a profoundly cynical view of the world.	
Schizoid	**Voluntary** social withdrawal (**A**loof), limited emotional expression, content with social isolation (vs avoidant).	
Schizotypal	Eccentric appearance, odd beliefs or magical thinking, interpersonal **A**wkwardness.	Schizo**t**ypal = magical **t**hinking.
Cluster B personality disorders	Dramatic, emotional, or erratic; genetic association with mood disorders and substance abuse.	“**Wild.**” Cluster **B**: **B**ad, **B**orderline, flam**B**oyant, must be the **B**est
Antisocial	Disregard for and violation of rights of others with lack of remorse, criminality, impulsivity; males > females; must be ≥ 18 years old and have history of conduct disorder before age 15. Conduct disorder if < 18 years old.	Anti**soci**al = **soci**opath. **B**ad.
Borderline	Unstable mood and interpersonal relationships, impulsivity, self-mutilation, suicidality, sense of emptiness; females > males; splitting is a major defense mechanism.	Treatment: dialectical behavior therapy. **B**orderline.
Histrionic	Excessive emotionality and excitability, attention seeking, sexually provocative, overly concerned with appearance.	Flam**B**oyant.
Narcissistic	Grandiosity, sense of entitlement; lacks empathy and requires excessive admiration; often demands the “best” and reacts to criticism with rage.	Must be the **B**est.
Cluster C personality disorders	Anxious or fearful; genetic association with anxiety disorders.	“**Worried.**” Cluster **C**: **C**owardly, obsessive-**C**ompulsive, **C**lingy.
Avoidant	Hypersensitive to rejection, socially inhibited, timid, feelings of inadequacy, desires relationships with others (vs schizoid).	**C**owardly.
Obsessive-Compulsive	Preoccupation with order, perfectionism, and control; ego-syntonic: behavior consistent with one’s own beliefs and attitudes (vs OCD).	
Dependent	Submissive and **C**lingy, excessive need to be taken care of, low self-confidence.	Patients often get stuck in abusive relationships.

Malingering	Patient **consciously** fakes, profoundly exaggerates, or claims to have a disorder in order to attain a specific **2° (external) gain** (eg, avoiding work, obtaining compensation). Poor compliance with treatment or follow-up of diagnostic tests. Complaints cease after gain (vs factitious disorder).

Factitious disorders	Patient **consciously** creates physical and/or psychological symptoms in order to assume "sick role" and to get medical attention and sympathy (**1° [internal] gain**).
Factitious disorder imposed on self	Also known as Munchausen syndrome. **Chronic** factitious disorder with predominantly physical signs and symptoms. Characterized by a history of multiple hospital admissions and willingness to undergo invasive procedures. More common in women and healthcare workers.
Factitious disorder imposed on another	Also known as Munchausen syndrome by proxy. Illness in a child or elderly patient is caused or fabricated by the caregiver. Motivation is to assume a sick role by proxy. Form of child/elder abuse.

Somatic symptom and related disorders	Category of disorders characterized by physical symptoms causing significant distress and impairment. Both illness production and motivation are **unconscious** drives. Symptoms not intentionally produced or feigned. More common in women.
Somatic symptom disorder	Variety of bodily complaints (eg, pain, fatigue) lasting for months to years. Associated with excessive, persistent thoughts and anxiety about symptoms. May co-occur with medical illness. Treatment: regular office visits with the same physician in combination with psychotherapy.
Conversion disorder (functional neurologic symptom disorder)	Loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient is aware of but sometimes indifferent toward symptoms ("la belle indifférence"); more common in females, adolescents, and young adults.
Illness anxiety disorder (hypochondriasis)	Excessive preoccupation with acquiring or having a serious illness, often despite medical evaluation and reassurance; minimal somatic symptoms.

Eating disorders	Most common in young females.
Anorexia nervosa	Excessive dieting, exercise, or binge eating/purging with BMI < 18.5 kg/m^2; intense fear of gaining weight; and distortion or overvaluation of body image. Associated with ↓ bone density, severe weight loss, metatarsal stress fractures, amenorrhea (due to loss of pulsatile GnRH secretion), lanugo, anemia, electrolyte disturbances. Commonly coexists with depression. Psychotherapy and nutritional rehabilitation are first line; pharmacotherapy includes SSRIs. Refeeding syndrome (↑ insulin → hypophosphatemia → cardiac complications) can occur in significantly malnourished patients.
Bulimia nervosa	Binge eating with recurrent inappropriate compensatory behaviors (eg, self-induced vomiting, using laxatives or diuretics, fasting, excessive exercise) occurring weekly for at least 3 months and overvaluation of body image. Body weight often maintained within normal range. Associated with parotitis, enamel erosion, electrolyte disturbances (eg, hypokalemia, hypochloremia), metabolic alkalosis, dorsal hand calluses from induced vomiting (Russell sign). Treatment: psychotherapy, nutritional rehabilitation, antidepressants.
Binge eating disorder	Regular episodes of excessive, uncontrollable eating without inappropriate compensatory behaviors. ↑ risk of diabetes. Treatment: psychotherapy such as CBT is first-line; SSRIs, lisdexamfetamine.
Gender dysphoria	Persistent cross-gender identification that leads to persistent distress with sex assigned at birth. **Transsexualism**—desire to live as the opposite sex, often through surgery or hormone treatment. **Transvestism**—paraphilia, not gender dysphoria. Wearing clothes (eg, vest) of the opposite sex (cross-dressing).
Sexual dysfunction	Includes sexual desire disorders (hypoactive sexual desire or sexual aversion), sexual arousal disorders (erectile dysfunction), orgasmic disorders (anorgasmia, premature ejaculation), sexual pain disorders (dyspareunia, vaginismus). Differential diagnosis includes: ▪ Drug side effects (eg, antihypertensives, antipsychotics, SSRIs, ethanol) ▪ Medical disorders (eg, depression, diabetes, STIs) ▪ Psychological (eg, performance anxiety)

Sleep terror disorder

Inconsolable periods of terror with screaming in the middle of the night; occurs during slow-wave/deep (stage N3) sleep. Most common in children. Occurs during non-REM sleep (no memory of the arousal episode) as opposed to nightmares that occur during REM sleep (memory of a scary dream). Cause unknown, but triggers include emotional stress, fever, or lack of sleep. Usually self limited.

Narcolepsy

Disordered regulation of sleep-wake cycles; 1° characteristic is excessive daytime sleepiness (awaken feeling rested).

Caused by ↓ hypocretin (orexin) production in lateral hypothalamus.

Also associated with:

- Hypnagogic (just before sleep) or hypnopompic (just before awakening) hallucinations.
- Nocturnal and narcoleptic sleep episodes that start with REM sleep (sleep paralysis).
- Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter) in some patients.

Strong genetic component. Treatment: daytime stimulants (eg, amphetamines, modafinil) and nighttime sodium oxybate (GHB).

Hypna**go**gic—**go**ing to sleep
Hypno**pomp**ic—“**pomp**ous upon awakening”

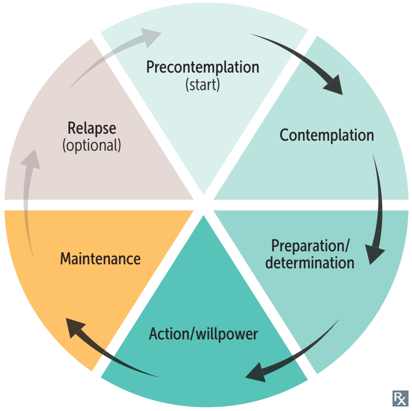
Substance use disorder

Maladaptive pattern of substance use defined as 2 or more of the following signs in 1 year related specifically to substance use:

- Tolerance—need more to achieve same effect
- Withdrawal—manifesting as characteristic signs and symptoms
- Substance taken in larger amounts, or over longer time, than desired
- Persistent desire or unsuccessful attempts to cut down
- Significant energy spent obtaining, using, or recovering from substance
- Important social, occupational, or recreational activities reduced
- Continued use despite knowing substance causes physical and/or psychological problems
- Craving
- Recurrent use in physically dangerous situations
- Failure to fulfill major obligations at work, school, or home
- Social or interpersonal conflicts

Stages of change in overcoming substance addiction

1. **Precontemplation**—not yet acknowledging that there is a problem
2. **Contemplation**—acknowledging that there is a problem, but not yet ready or willing to make a change
3. **Preparation/determination**—getting ready to change behaviors
4. **Action/willpower**—changing behaviors
5. **Maintenance**—maintaining the behavioral changes
6. **Relapse**—returning to old behaviors and abandoning new changes. Does not always happen.


Precontemplation (start)
Contemplation
Preparation/ determination
Action/willpower
Maintenance
Relapse (optional)
℞

Psychoactive drug intoxication and withdrawal

DRUG	INTOXICATION	WITHDRAWAL
Depressants		
	Nonspecific: mood elevation, ↓ anxiety, sedation, behavioral disinhibition, respiratory depression.	Nonspecific: anxiety, tremor, seizures, insomnia.
Alcohol	Emotional lability, slurred speech, ataxia, coma, blackouts. Serum γ-glutamyltransferase (GGT)—sensitive indicator of alcohol use. AST value is twice ALT value.	Time from last drink: 3–36 hr: minor symptoms similar to other depressants 6–48 hr: withdrawal seizures 12–48 hr: alcoholic hallucinosis (usually visual) 48–96 hr: delirium tremens (DTs) in 5% of cases Treatment: benzodiazepines.
Opioids	Euphoria, respiratory and CNS depression, ↓ gag reflex, pupillary constriction (pinpoint pupils), seizures (overdose). Most common cause of drug overdose death. Treatment: naloxone.	Sweating, dilated pupils, piloerection (“cold turkey”), fever, rhinorrhea, yawning, nausea, stomach cramps, diarrhea (“flu-like” symptoms). Treatment: long-term support, methadone, buprenorphine.
Barbiturates	Low safety margin, marked respiratory depression. Treatment: symptom management (eg, assist respiration, ↑ BP).	Delirium, life-threatening cardiovascular collapse.
Benzodiazepines	Greater safety margin. Ataxia, minor respiratory depression. Treatment: flumazenil (benzodiazepine receptor antagonist, but rarely used as it can precipitate seizures).	Sleep disturbance, depression, rebound anxiety, seizure.
Stimulants		
	Nonspecific: mood elevation, psychomotor agitation, insomnia, cardiac arrhythmias, tachycardia, anxiety.	Nonspecific: post-use “crash,” including depression, lethargy, ↑ appetite, sleep disturbance, vivid nightmares.
Amphetamines	Euphoria, grandiosity, pupillary dilation, prolonged wakefulness and attention, hypertension, tachycardia, anorexia, paranoia, fever. Severe: cardiac arrest, seizures. Treatment: benzodiazepines for agitation and seizures.	
Cocaine	Impaired judgment, pupillary dilation, hallucinations (including tactile), paranoid ideations, angina, sudden cardiac death. Treatment: α-blockers, benzodiazepines. β-blockers not recommended.	
Caffeine	Restlessness, ↑ diuresis, muscle twitching.	Headache, difficulty concentrating, flu-like symptoms.
Nicotine	Restlessness.	Irritability, anxiety, restlessness, difficulty concentrating. Treatment: nicotine patch, gum, or lozenges; bupropion/varenicline.

Psychoactive drug intoxication and withdrawal *(continued)*

DRUG	INTOXICATION	WITHDRAWAL
Hallucinogens		
Phencyclidine	Violence, impulsivity, psychomotor agitation, nystagmus, tachycardia, hypertension, analgesia, psychosis, delirium, seizures. Trauma is most common complication. Treatment: benzodiazepines, rapid-acting antipsychotic.	
Lysergic acid diethylamide (LSD)	Perceptual distortion (visual, auditory), depersonalization, anxiety, paranoia, psychosis, possible flashbacks.	
Marijuana (cannabinoid)	Euphoria, anxiety, paranoid delusions, perception of slowed time, impaired judgment, social withdrawal, ↑ appetite, dry mouth, conjunctival injection, hallucinations. Pharmaceutical form is dronabinol: used as antiemetic (chemotherapy) and appetite stimulant (in AIDS).	Irritability, anxiety, depression, insomnia, restlessness, ↓ appetite.
MDMA (ecstasy)	Hallucinogenic stimulant: euphoria, disinhibition, hyperactivity, distorted sensory and time perception, teeth clenching. Life-threatening effects include hypertension, tachycardia, hyperthermia, hyponatremia, serotonin syndrome.	Depression, fatigue, change in appetite, difficulty concentrating, anxiety.

Heroin detoxification medications	Users at ↑ risk for hepatitis, HIV, abscesses, bacteremia, right-heart endocarditis.
Methadone	Long-acting oral opiate used for heroin detoxification or long-term maintenance therapy.
Buprenorphine + naloxone	Sublingually, buprenorphine (partial agonist) is absorbed and used for maintenance therapy. Naloxone (antagonist, not orally bioavailable) is added to lower IV abuse potential.
Naltrexone	Long-acting opioid antagonist used for relapse prevention once detoxified.

Alcoholism	Physiologic tolerance and dependence on alcohol with symptoms of withdrawal when intake is interrupted. Complications: alcoholic cirrhosis, hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy. Treatment: disulfiram (to condition the patient to abstain from alcohol use), acamprosate, naltrexone, supportive care. Support groups such as Alcoholics Anonymous are helpful in sustaining abstinence and supporting patient and family.
Wernicke-Korsakoff syndrome	Caused by vitamin B_1 deficiency. Triad of confusion, ophthalmoplegia, ataxia (Wernicke encephalopathy). May progress to irreversible memory loss, confabulation, personality change (Korsakoff syndrome). Symptoms may be precipitated by giving dextrose before administering vitamin B_1 to a patient with thiamine deficiency. Associated with periventricular hemorrhage/necrosis of mammillary bodies. Treatment: IV vitamin B_1.

Delirium tremens

Life-threatening alcohol withdrawal syndrome that peaks 2–4 days after last drink.

Characterized by autonomic hyperactivity (eg, tachycardia, tremors, anxiety, seizures), electrolyte disturbances, respiratory alkalosis. Classically occurs in hospital setting (eg, 2–4 days postsurgery) in alcoholics not able to drink as inpatients. Treatment: benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam).

▸ PSYCHIATRY—PHARMACOLOGY

Preferred medications for selected psychiatric conditions

PSYCHIATRIC CONDITION	PREFERRED DRUGS
ADHD	Stimulants (methylphenidate, amphetamines)
Alcohol withdrawal	Benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam)
Bipolar disorder	Lithium, valproic acid, carbamazepine, lamotrigine, atypical antipsychotics
Bulimia nervosa	SSRIs
Depression	SSRIs
Generalized anxiety disorder	SSRIs, SNRIs
Obsessive-compulsive disorder	SSRIs, venlafaxine, clomipramine
Panic disorder	SSRIs, venlafaxine, benzodiazepines
PTSD	SSRIs, venlafaxine
Schizophrenia	Atypical antipsychotics
Social anxiety disorder	SSRIs, venlafaxine Performance only: β-blockers, benzodiazepines
Tourette syndrome	Antipsychotics (eg, fluphenazine, pimozide), tetrabenazine

Central nervous system stimulants	Methylphenidate, dextroamphetamine, methamphetamine.
MECHANISM	↑ catecholamines in the synaptic cleft, especially norepinephrine and dopamine.
CLINICAL USE	ADHD, narcolepsy, appetite control.
ADVERSE EFFECTS	Nervousness, agitation, anxiety, insomnia, anorexia, tachycardia, hypertension.

Typical antipsychotics	Haloperidol, pimozide, trifluoperazine, fluphenazine, thioridazine, chlorpromazine.
MECHANISM	Block dopamine D_2 receptor (↑ cAMP).
CLINICAL USE	Schizophrenia (1° positive symptoms), psychosis, bipolar disorder, delirium, Tourette syndrome, Huntington disease, OCD.
POTENCY	High potency: Trifluoperazine, Fluphenazine, Haloperidol (Try to Fly High)—neurologic side effects (eg, extrapyramidal symptoms [EPS]). Low potency: Chlorpromazine, Thioridazine (Cheating Thieves are low)—anticholinergic, antihistamine, α_1-blockade effects.
ADVERSE EFFECTS	Lipid soluble → stored in body fat → slow to be removed from body. Endocrine: dopamine receptor antagonism → hyperprolactinemia → galactorrhea, oligomenorrhea, gynecomastia. Metabolic: dyslipidemia, weight gain, hyperglycemia. Antimuscarinic: dry mouth, constipation. Antihistamine: sedation. α_1-blockade: orthostatic hypotension. Cardiac: QT prolongation. Ophthalmologic: Chlorpromazine—Corneal deposits; Thioridazine—reTinal deposits. **EPS—ADAPT:** ▪ Hours to days: Acute Dystonia (muscle spasm, stiffness, oculogyric crisis). ▪ Days to months: Akathisia (restlessness), Parkinsonism (bradykinesia). ▪ Months to years: Tardive dyskinesia (orofacial chorea). Treatment: benztropine (acute dystonia, tardive dyskinesia), benzodiazepines, β-blockers (akathisia). **Neuroleptic malignant syndrome (NMS)**—Malignant FEVER: Myoglobinuria, Fever, Encephalopathy, unstable Vitals, ↑ Enzymes, muscle Rigidity. Treatment: dantrolene, D_2 agonist (eg, bromocriptine).

Atypical antipsychotics	Aripiprazole, asenapine, clozapine, olanzapine, quetiapine, iloperidone, paliperidone, risperidone, lurasidone, ziprasidone.	
MECHANISM	Not completely understood. Most are D_2 antagonists; aripiprazole is D_2 partial agonist. Varied effects on 5-HT_2, dopamine, and α- and H_1-receptors.	
CLINICAL USE	Schizophrenia—both positive and negative symptoms. Also used for bipolar disorder, OCD, anxiety disorder, depression, mania, Tourette syndrome.	Use clozapine for treatment-resistant schizophrenia or schizoaffective disorder and for suicidality in schizophrenia.
ADVERSE EFFECTS	All—prolonged QT interval, fewer EPS and anticholinergic side effects than typical antipsychotics.	
	"-pines"—metabolic syndrome (weight gain, diabetes, hyperlipidemia).	Olanzapine → Obesity
	Clozapine—agranulocytosis (monitor WBCs frequently) and seizures (dose related).	Must watch bone marrow clozely with clozapine.
	Risperidone—hyperprolactinemia (amenorrhea, galactorrhea, gynecomastia).	

Lithium

MECHANISM	Not established; possibly related to inhibition of phosphoinositol cascade.
CLINICAL USE	Mood stabilizer for bipolar disorder; blocks relapse and acute manic events.
ADVERSE EFFECTS	Tremor, hypothyroidism, polyuria (causes nephrogenic diabetes insipidus), teratogenesis. Causes Ebstein anomaly in newborn if taken by pregnant mother. Narrow therapeutic window requires close monitoring of serum levels. Almost exclusively excreted by kidneys; most is reabsorbed at PCT with Na^+. Thiazides (and other nephrotoxic agents) are implicated in lithium toxicity.

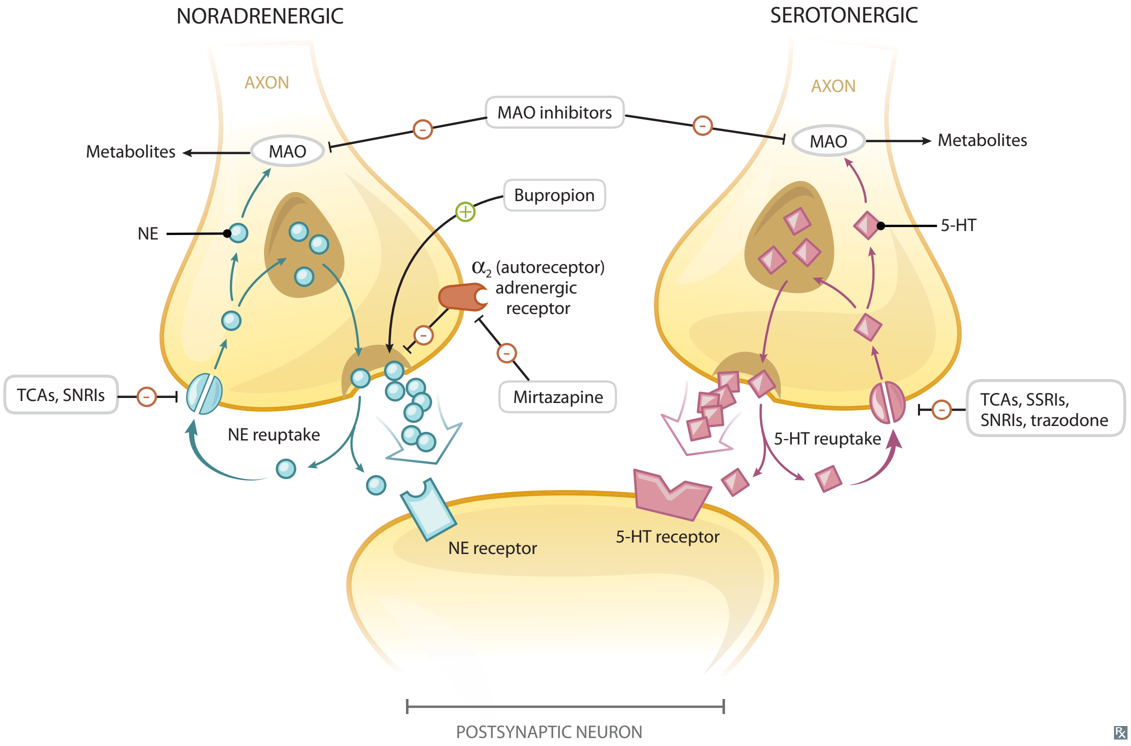
LiTHIUM:
Low **T**hyroid (hypothyroidism)
Heart (Ebstein anomaly)
Insipidus (nephrogenic diabetes insipidus)
Unwanted **M**ovements (tremor)

Buspirone

MECHANISM	Stimulates 5-HT_{1A} receptors.
CLINICAL USE	Generalized anxiety disorder. Does not cause sedation, addiction, or tolerance. Takes 1–2 weeks to take effect. Does not interact with alcohol (vs barbiturates, benzodiazepines).

I'm always anxious if the **bus** will be **on** time, so I take **buspirone**.

Antidepressants


NORADRENERGIC
SEROTONERGIC
AXON
AXON
MAO inhibitors
Metabolites
MAO
MAO
Metabolites
Bupropion
NE
5-HT
α2 (autoreceptor) adrenergic receptor
Mirtazapine
TCAs, SNRIs
NE reuptake
TCAs, SSRIs, SNRIs, trazodone
5-HT reuptake
NE receptor
5-HT receptor
POSTSYNAPTIC NEURON

Selective serotonin reuptake inhibitors

Fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram, citalopram.

MECHANISM	Inhibit 5-HT reuptake.
CLINICAL USE	Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder.
ADVERSE EFFECTS	Fewer than TCAs. GI distress, SIADH, sexual dysfunction (anorgasmia, ↓ libido).

It normally takes 4–8 weeks for antidepressants to have an effect.

Serotonin-norepinephrine reuptake inhibitors

Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, milnacipran.

MECHANISM	Inhibit 5-HT and norepinephrine reuptake.
CLINICAL USE	Depression, general anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD. Duloxetine is also indicated for fibromyalgia.
ADVERSE EFFECTS	↑ BP most common; also stimulant effects, sedation, nausea.

Serotonin syndrome

Can occur with any drug that ↑ 5-HT (eg, MAOIs, SSRIs, SNRIs, TCAs, tramadol, ondansetron, triptans, linezolid, MDMA, dextromethorphan). Characterized by **3 A's**: neuromuscular hyper**A**ctivity (clonus, hyperreflexia, hypertonia, tremor, seizure), **A**utonomic stimulation (hyperthermia, diaphoresis, diarrhea), and **A**gitation. Treatment: cyproheptadine (5-HT_2 receptor antagonist).

Tricyclic antidepressants

Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, amoxapine.

MECHANISM	Inhibit NE and 5-HT reuptake.
CLINICAL USE	Major depression, OCD (clomipramine), peripheral neuropathy, chronic pain, migraine prophylaxis. Nocturnal enuresis (imipramine, although adverse effects may limit use).
ADVERSE EFFECTS	Sedation, α_1-blocking effects including postural hypotension, and atropine-like (anticholinergic) side effects (tachycardia, urinary retention, dry mouth). 3° TCAs (amitriptyline) have more anticholinergic effects than 2° TCAs (nortriptyline). Can prolong QT interval. **Tri-C's**: **C**onvulsions, **C**oma, **C**ardiotoxicity (arrhythmia due to Na^+ channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations in elderly due to anticholinergic side effects (nortriptyline better tolerated in the elderly). Treatment: $NaHCO_3$ to prevent arrhythmia.

Monoamine oxidase inhibitors	Tranylcypromine, Phenelzine, Isocarboxazid, Selegiline (selective MAO-B inhibitor). (MAO Takes Pride In Shanghai).
MECHANISM	Nonselective MAO inhibition ↑ levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine).
CLINICAL USE	Atypical depression, anxiety. Parkinson disease (selegiline).
ADVERSE EFFECTS	CNS stimulation; hypertensive crisis, most notably with ingestion of tyramine, which is found in many foods such as aged cheese and wine. Tyramine displaces other neurotransmitters (eg, NE) into the synaptic cleft → ↑ sympathetic stimulation. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan (to prevent serotonin syndrome). Wait 2 weeks after stopping MAO inhibitors before starting serotonergic drugs or stopping dietary restrictions.

Atypical antidepressants	
Bupropion	Inhibits reuptake of NE and dopamine. Also used for smoking cessation. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in anorexic/bulimic patients. May help alleviate sexual dysfunction.
Mirtazapine	α_2-antagonist (↑ release of NE and 5-HT), potent 5-HT_2 and 5-HT_3 receptor antagonist and H_1 antagonist. Toxicity: sedation (which may be desirable in depressed patients with insomnia), ↑ appetite, weight gain (which may be desirable in elderly or anorexic patients), dry mouth.
Trazodone	Primarily blocks 5-HT_2, α_1-adrenergic, and H_1 receptors; also weakly inhibits 5-HT reuptake. Used primarily for insomnia, as high doses are needed for antidepressant effects. Toxicity: sedation, nausea, priapism, postural hypotension. Called traZZZobone due to sedative and male-specific side effects.
Varenicline	Nicotinic ACh receptor partial agonist. Used for smoking cessation. Toxicity: sleep disturbance, may depress mood.
Vilazodone	Inhibits 5-HT reuptake; 5-HT_{1A} receptor partial agonist. Used for major depressive disorder and generalized anxiety disorder (off-label). Toxicity: headache, diarrhea, nausea, ↑ weight, anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.
Vortioxetine	Inhibits 5-HT reuptake; 5-HT_{1A} receptor agonist and 5-HT_3 receptor antagonist. Used for major depressive disorder. Toxicity: nausea, sexual dysfunction, sleep disturbances (abnormal dreams), anticholinergic effects. May cause serotonin syndrome if taken with other serotonergic agents.

HIGH-YIELD SYSTEMS

Renal

"But I know all about love already. I know precious little still about kidneys."

—Aldous Huxley, *Antic Hay*

"This too shall pass. Just like a kidney stone."

—Hunter Madsen

"I drink too much. The last time I gave a urine sample it had an olive in it."

—Rodney Dangerfield

- Embryology 548
- Anatomy 550
- Physiology 551
- Pathology 562
- Pharmacology 574

▸ RENAL—EMBRYOLOGY

Kidney embryology

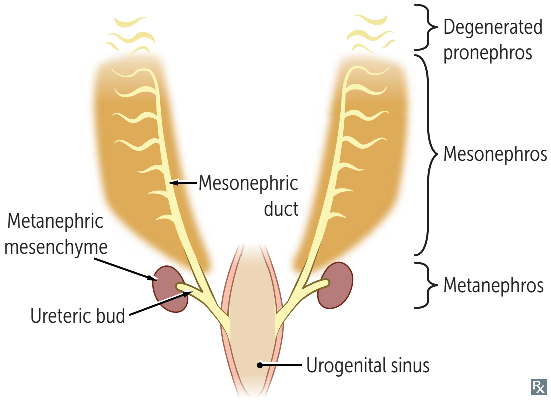
Pronephros—week 4; then degenerates.

Mesonephros—functions as interim kidney for 1st trimester; later contributes to male genital system.

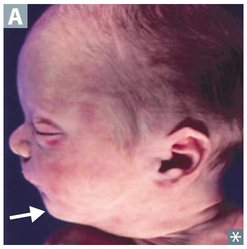
Metanephros—permanent; first appears in 5th week of gestation; nephrogenesis continues through weeks 32–36 of gestation.

- Ureteric bud—derived from caudal end of mesonephric duct; gives rise to ureter, pelvises, calyces, collecting ducts; fully canalized by 10th week
- Metanephric mesenchyme (ie, metanephric blastema)—ureteric bud interacts with this tissue; interaction induces differentiation and formation of glomerulus through to distal convoluted tubule (DCT)
- Aberrant interaction between these 2 tissues may result in several congenital malformations of the kidney

Ureteropelvic junction—last to canalize → most common site of obstruction (can be detected on prenatal ultrasound as hydronephrosis).



Potter sequence (syndrome)



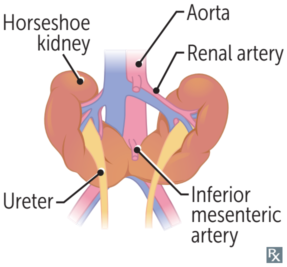
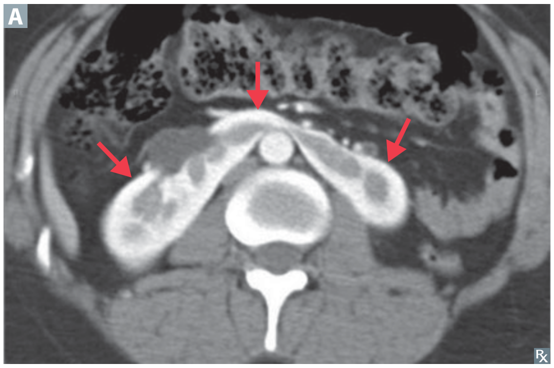
Oligohydramnios → compression of developing fetus → limb deformities, facial anomalies (eg, low-set ears and retrognathia A, flattened nose), compression of chest and lack of amniotic fluid aspiration into fetal lungs → pulmonary hypoplasia (cause of death).

Causes include ARPKD, obstructive uropathy (eg, posterior urethral valves), bilateral renal agenesis, chronic placental insufficiency.

Babies who can't "**P**ee" in utero develop **P**otter sequence.

POTTER sequence associated with:

- **P**ulmonary hypoplasia
- **O**ligohydramnios (trigger)
- **T**wisted face
- **T**wisted skin
- **E**xtremity defects
- **R**enal failure (in utero)

Horseshoe kidney  Horseshoe kidney Aorta Renal artery Ureter Inferior mesenteric artery	Inferior poles of both kidneys fuse abnormally A. As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. Kidneys function normally. Associated with hydronephrosis (eg, ureteropelvic junction obstruction), renal stones, infection, chromosomal aneuploidy syndromes (eg, Turner syndrome; trisomies 13, 18, 21), and rarely renal cancer. 
Congenital solitary functioning kidney	Condition of being born with only one functioning kidney. Majority asymptomatic with compensatory hypertrophy of contralateral kidney, but anomalies in contralateral kidney are common. Often diagnosed prenatally via ultrasound.
Unilateral renal agenesis	Ureteric bud fails to develop and induce differentiation of metanephric mesenchyme → complete absence of kidney and ureter.
Multicystic dysplastic kidney	Ureteric bud fails to induce differentiation of metanephric mesenchyme → nonfunctional kidney consisting of cysts and connective tissue. Predominantly nonhereditary and usually unilateral; bilateral leads to Potter sequence.
Duplex collecting system	Bifurcation of ureteric bud before it enters the metanephric blastema creates a Y-shaped bifid ureter. Duplex collecting system can alternatively occur through two ureteric buds reaching and interacting with metanephric blastema. Strongly associated with vesicoureteral reflux and/or ureteral obstruction, ↑ risk for UTIs.
Posterior urethral valves	Membrane remnant in the posterior urethra in males; its persistence can lead to urethral obstruction. Can be diagnosed prenatally by hydronephrosis and dilated or thick-walled bladder on ultrasound. Most common cause of bladder outlet obstruction in male infants.

▶ RENAL—ANATOMY

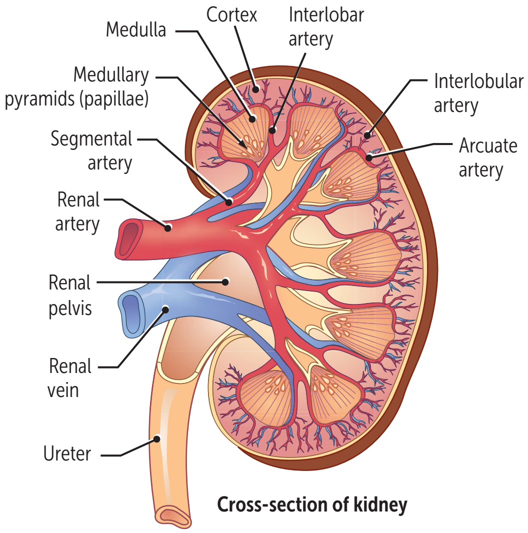
Kidney anatomy and glomerular structure

Left kidney is taken during donor transplantation because it has a longer renal vein.

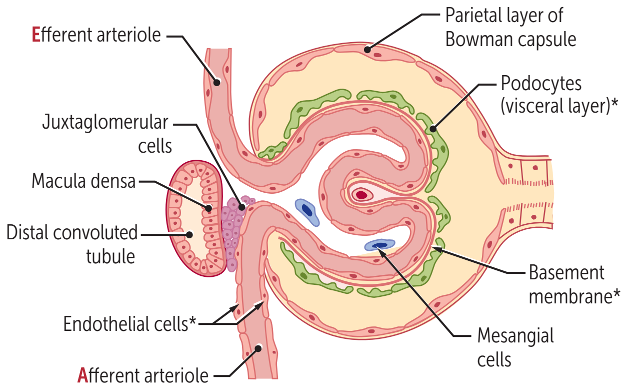
Afferent = Arriving.

Efferent = Exiting.

Renal blood flow: renal artery → segmental artery → interlobar artery → arcuate artery → interlobular artery → afferent arteriole → glomerulus → efferent arteriole → vasa recta/peritubular capillaries → venous outflow.

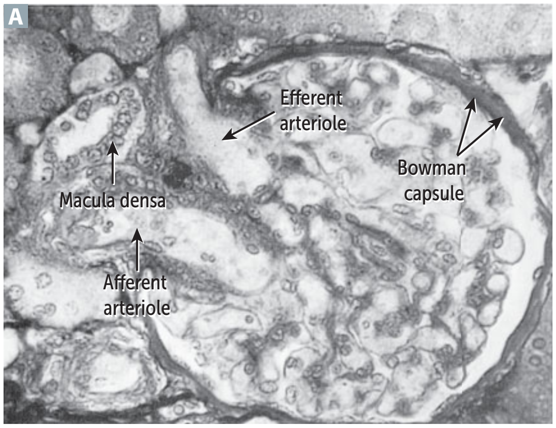

Medulla
Cortex
Interlobar artery
Medullary pyramids (papillae)
Interlobular artery
Segmental artery
Arcuate artery
Renal artery
Renal pelvis
Renal vein
Ureter

Cross-section of kidney

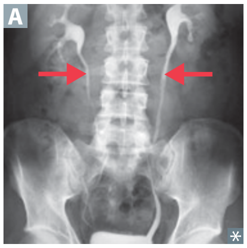

Efferent arteriole
Parietal layer of Bowman capsule
Podocytes (visceral layer)*
Juxtaglomerular cells
Macula densa
Distal convoluted tubule
Basement membrane*
Endothelial cells*
Mesangial cells
Afferent arteriole

*Components of glomerular filtration barrier.

Cross-section of glomerulus A


A
Efferent arteriole
Macula densa
Bowman capsule
Afferent arteriole

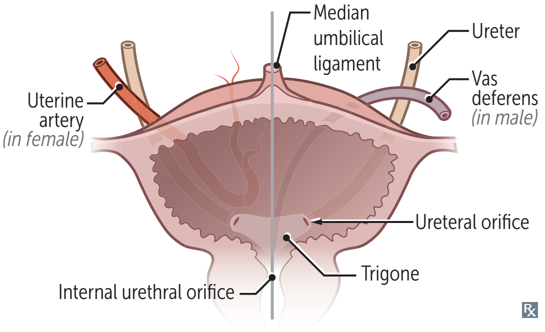
Course of ureters



Ureters A pass under uterine artery or under vas deferens (retroperitoneal).

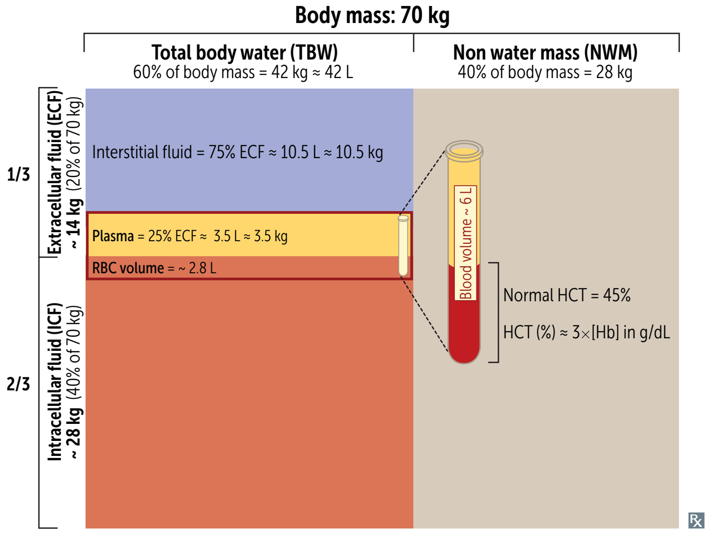
Gynecologic procedures (eg, ligation of uterine or ovarian vessels) may damage ureter → ureteral obstruction or leak.

"Water (ureters) under the bridge (uterine artery or vas deferens)."


Median umbilical ligament
Ureter
Vas deferens (in male)
Uterine artery (in female)
Ureteral orifice
Trigone
Internal urethral orifice

▸ RENAL—PHYSIOLOGY

Fluid compartments


Body mass: 70 kg
Total body water (TBW)
60% of body mass = 42 kg ≈ 42 L
Non water mass (NWM)
40% of body mass = 28 kg
1/3
Extracellular fluid (ECF)
~ 14 kg (20% of 70 kg)
2/3
Intracellular fluid (ICF)
~ 28 kg (40% of 70 kg)
Interstitial fluid = 75% ECF ≈ 10.5 L ≈ 10.5 kg
Plasma = 25% ECF ≈ 3.5 L ≈ 3.5 kg
RBC volume = ~ 2.8 L
Blood volume ~ 6 L
Normal HCT = 45%
HCT (%) ≈ 3×[Hb] in g/dL

HIKIN': **HI**gh **K$^+$** **IN**tracellularly.

60–40–20 rule (% of body weight for average person):

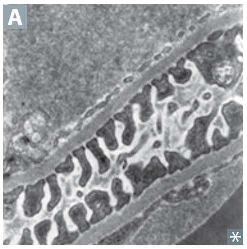
- 60% total body water
- 40% ICF
- 20% ECF

Plasma volume can be measured by radiolabeling albumin.

Extracellular volume can be measured by inulin or mannitol.

Osmolality = 285–295 mOsm/kg H_2O.

Glomerular filtration barrier



Responsible for filtration of plasma according to size and charge selectivity.

Composed of:

- Fenestrated capillary endothelium
- Basement membrane with type IV collagen chains and heparan sulfate
- Epithelial layer consisting of podocyte foot processes A

Charge barrier—all 3 layers contain ⊖ charged glycoproteins preventing ⊕ charged molecule entry (eg, albumin).

Size barrier—fenestrated capillary epithelium (prevent entry of > 100 nm molecules/blood cells); podocyte foot processes interpose with basement membrane; slit diaphragm (prevent entry of molecules > 50–60 nm).

Renal clearance

$C_x = U_x V/P_x$ = volume of plasma from which the substance is completely cleared per unit time.
If $C_x <$ GFR: net tubular reabsorption of X.
If $C_x >$ GFR: net tubular secretion of X.
If $C_x =$ GFR: no net secretion or reabsorption.

C_x = clearance of X (mL/min).
U_x = urine concentration of X (eg, mg/mL).
P_x = plasma concentration of X (eg, mg/mL).
V = urine flow rate (mL/min).

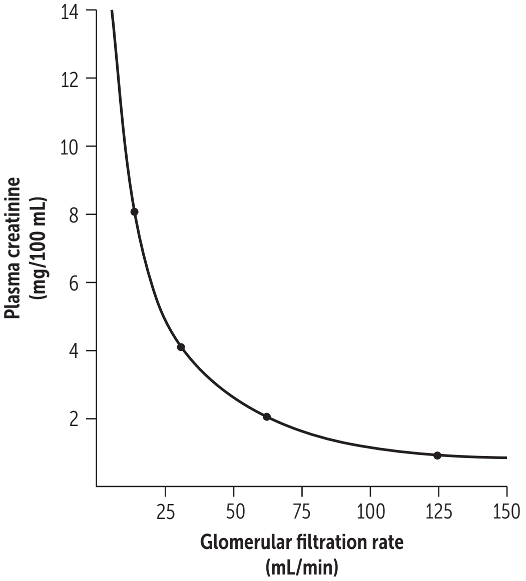
Glomerular filtration rate

Inulin clearance can be used to calculate GFR because it is freely filtered and is neither reabsorbed nor secreted.

$$\begin{aligned} \text{GFR} &= U_{\text{inulin}} \times V/P_{\text{inulin}} = C_{\text{inulin}} \\ &= K_f\,[(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})] \end{aligned}$$

(GC = glomerular capillary; BS = Bowman space.) π_{BS} normally equals zero; K_f = filtration constant.

Normal GFR ≈ 100 mL/min.
Creatinine clearance is an approximate measure of GFR. Slightly overestimates GFR because creatinine is moderately secreted by renal tubules.
Incremental reductions in GFR define the stages of chronic kidney disease.



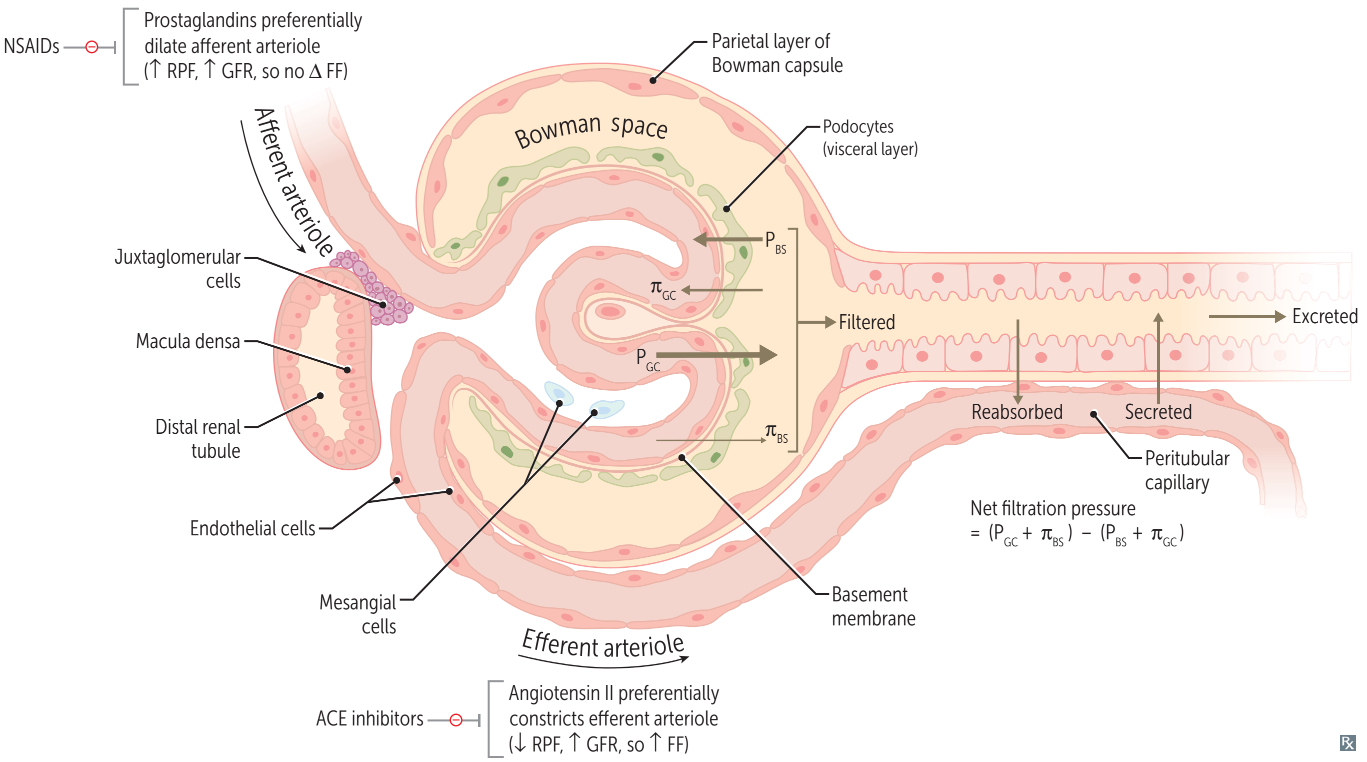
Effective renal plasma flow

Effective renal plasma flow (eRPF) can be estimated using *para*-aminohippuric acid (PAH) clearance. Between filtration and secretion, there is nearly 100% excretion of all PAH that enters the kidney.
$\text{eRPF} = U_{\text{PAH}} \times V/P_{\text{PAH}} = C_{\text{PAH}}$.
Renal blood flow (RBF) = RPF/(1 − Hct).
Plasma = 1 − hematocrit.
eRPF underestimates true renal plasma flow (RPF) slightly.

Filtration

Filtration fraction (FF) = GFR/RPF.
Normal FF = 20%.
Filtered load (mg/min) = GFR (mL/min) × plasma concentration (mg/mL).

GFR can be estimated with creatinine clearance.
RPF is best estimated with PAH clearance.
Prostaglandins **D**ilate **A**fferent arteriole (**PDA**)
ACE inhibitors **C**onstrict **E**fferent arteriole (**ACE**)


NSAIDs
Prostaglandins preferentially dilate afferent arteriole (↑ RPF, ↑ GFR, so no Δ FF)
Afferent arteriole
Parietal layer of Bowman capsule
Bowman space
Podocytes (visceral layer)
Juxtaglomerular cells
Macula densa
Distal renal tubule
Endothelial cells
Mesangial cells
P_{BS}
π_{GC}
P_{GC}
π_{BS}
Filtered
Excreted
Reabsorbed
Secreted
Peritubular capillary
Net filtration pressure = $(P_{GC} + \pi_{BS}) - (P_{BS} + \pi_{GC})$
Basement membrane
Efferent arteriole
ACE inhibitors
Angiotensin II preferentially constricts efferent arteriole (↓ RPF, ↑ GFR, so ↑ FF)

Changes in glomerular dynamics

Effect	GFR	RPF	FF (GFR/RPF)
Afferent arteriole constriction	↓	↓	—
Efferent arteriole constriction	↑	↓	↑
↑ plasma protein concentration	↓	—	↓
↓ plasma protein concentration	↑	—	↑
Constriction of ureter	↓	—	↓
Dehydration	↓	↓↓	↑

Calculation of reabsorption and secretion rate

Filtered load = GFR × P_x.
Excretion rate = V × U_x.
Reabsorption rate = filtered – excreted.
Secretion rate = excreted – filtered.

$$Fe_{Na} = \frac{Na^+ \text{ excreted}}{Na^+ \text{ filtered}} = \frac{V \times U_{Na}}{GFR\left(U_{Cr} \times \frac{V}{P_{Cr}}\right) \times P_{Na}} = \frac{P_{Cr} \times U_{Na}}{U_{Cr} \times P_{Na}}$$

Glucose clearance

Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by Na^+/glucose cotransport.

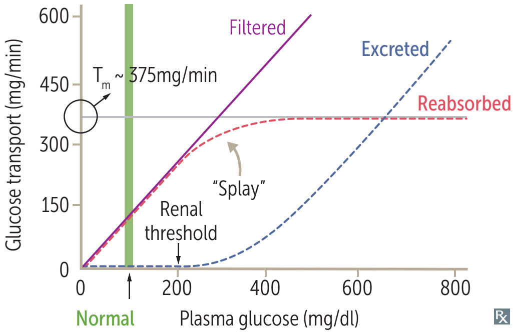
In adults, at plasma glucose of ~ 200 mg/dL, glucosuria begins (threshold). At rate of ~ 375 mg/min, all transporters are fully saturated (T_m).

Normal pregnancy may decrease ability of PCT to reabsorb glucose and amino acids → glucosuria and aminoaciduria.

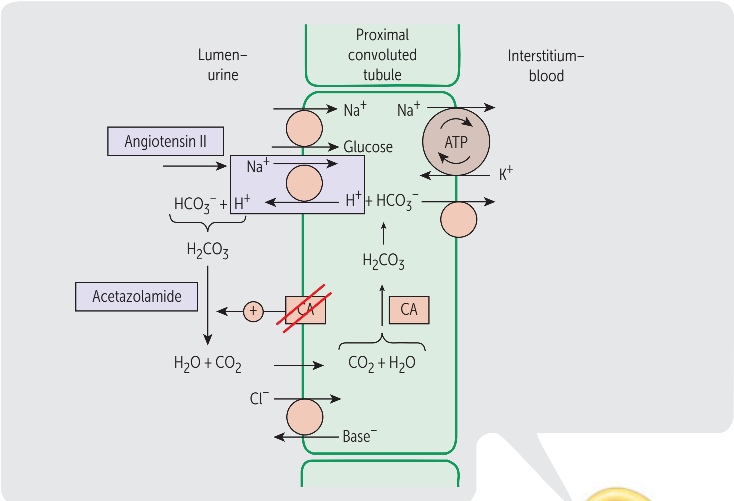
Sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, -flozin drugs) permit glucosuria at plasma concentrations < 200 mg/dL.

Glucosuria is an important clinical clue to diabetes mellitus.

Splay is the region of substance clearance between threshold and T_m; due to the heterogeneity of nephrons.



Nephron physiology


Lumen–urine
Proximal convoluted tubule
Interstitium–blood
Na+
Na+
ATP
Angiotensin II
Na+
Glucose
K+
HCO3− + H+
H+ + HCO3−
H2CO3
H2CO3
Acetazolamide
+
CA
CA
H2O + CO2
CO2 + H2O
Cl−
Base−

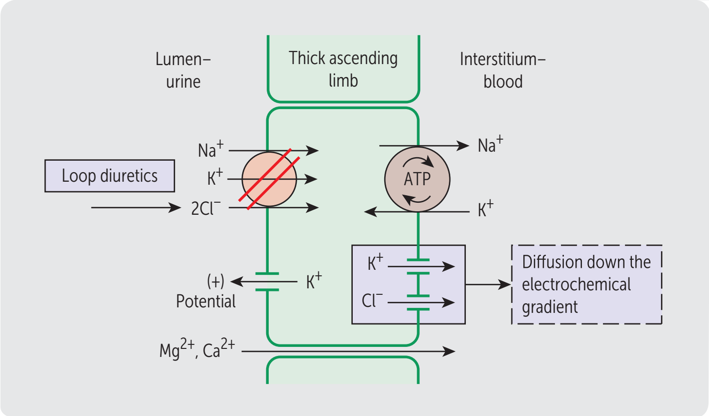
Early PCT—contains brush border. Reabsorbs all glucose and amino acids and most HCO_3^-, Na^+, Cl^-, PO_4^{3-}, K^+, H_2O, and uric acid. Isotonic absorption. Generates and secretes NH_3, which enables the kidney to secrete more H^+.

PTH—inhibits Na^+/PO_4^{3-} cotransport → PO_4^{3-} excretion.

AT II—stimulates Na^+/H^+ exchange → ↑ Na^+, H_2O, and HCO_3^- reabsorption (permitting contraction alkalosis).

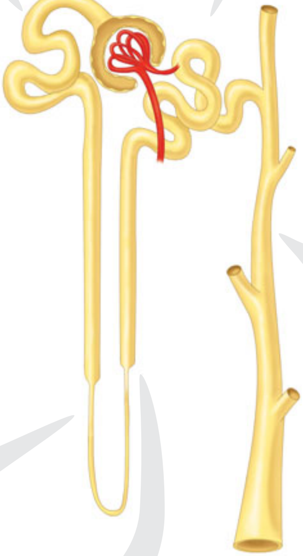
65–80% Na^+ reabsorbed.

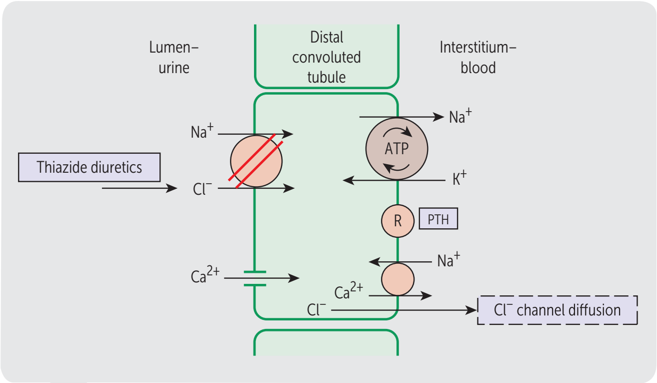
Thin descending loop of Henle—passively reabsorbs H_2O via medullary hypertonicity (impermeable to Na^+). Concentrating segment. Makes urine hypertonic.


Lumen–urine
Thick ascending limb
Interstitium–blood
Na+
Na+
Loop diuretics
K+
ATP
2Cl−
K+
K+
Cl−
Diffusion down the electrochemical gradient
(+) Potential
K+
Mg2+, Ca2+

Thick ascending loop of Henle—reabsorbs Na^+, K^+, and Cl^-. Indirectly induces paracellular reabsorption of Mg^{2+} and Ca^{2+} through ⊕ lumen potential generated by K^+ backleak. Impermeable to H_2O. Makes urine less concentrated as it ascends.

10–20% Na^+ reabsorbed.

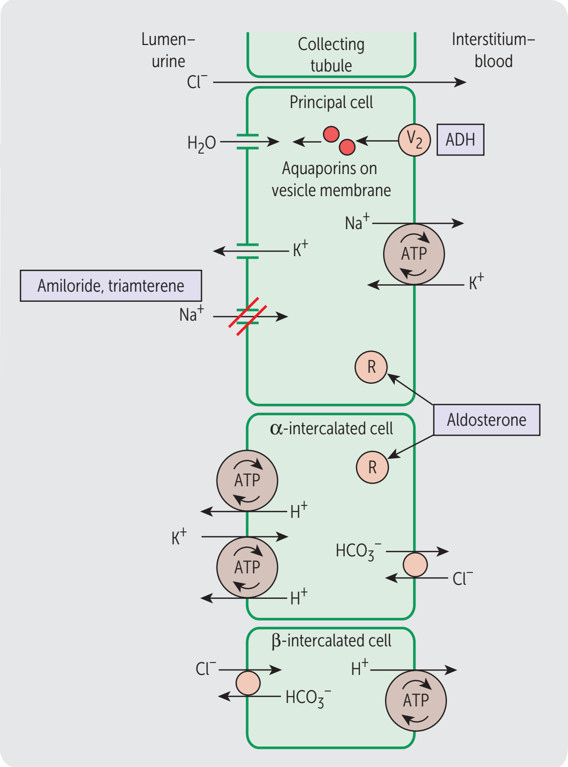



Lumen–urine
Distal convoluted tubule
Interstitium–blood
Na+
Na+
ATP
Thiazide diuretics
Cl−
K+
R
PTH
Na+
Ca2+
Ca2+
Cl−
Cl− channel diffusion

Early DCT—reabsorbs Na^+, Cl^-. Makes urine fully dilute (hypotonic).

PTH—↑ Ca^{2+}/Na^+ exchange → Ca^{2+} reabsorption.

5–10% Na^+ reabsorbed.


Lumen–urine
Collecting tubule
Interstitium–blood
Cl−
Principal cell
H2O
V2
ADH
Aquaporins on vesicle membrane
Na+
ATP
K+
K+
Amiloride, triamterene
Na+
R
Aldosterone
α-intercalated cell
ATP
R
H+
K+
HCO3−
ATP
Cl−
H+
β-intercalated cell
Cl−
H+
HCO3−
ATP

Collecting tubule—reabsorbs Na^+ in exchange for secreting K^+ and H^+ (regulated by aldosterone).

Aldosterone—acts on mineralocorticoid receptor → mRNA → protein synthesis. In principal cells: ↑ apical K^+ conductance, ↑ Na^+/K^+ pump, ↑ epithelial Na^+ channel (ENaC) activity → lumen negativity → K^+ secretion. In α-intercalated cells: lumen negativity → ↑ H^+ ATPase activity → ↑ H^+ secretion → ↑ HCO_3^-/Cl^- exchanger activity.

ADH—acts at V_2 receptor → insertion of aquaporin H_2O channels on apical side.

3–5% Na^+ reabsorbed.

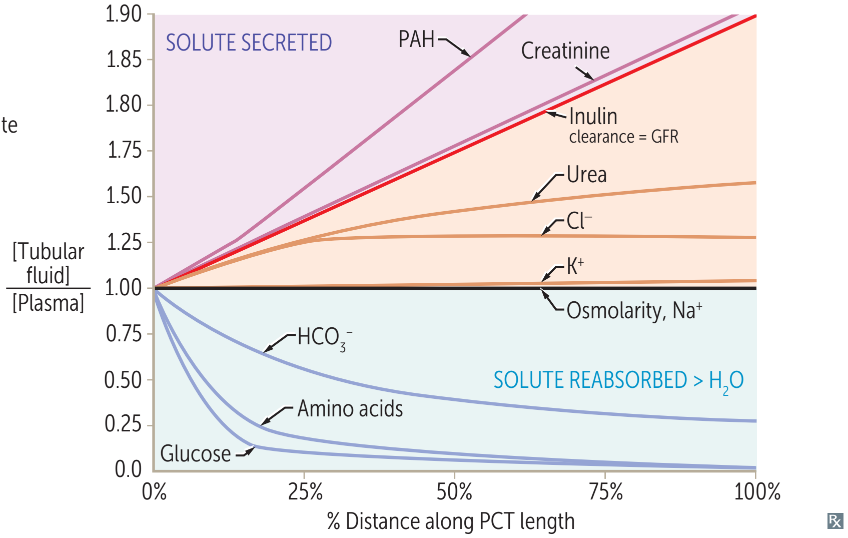
Renal tubular defects	Fanconi syndrome is first (PCT), the rest are in **alphabetic** order.
Fanconi syndrome	Generalized reabsorptive defect in PCT. Associated with ↑ excretion of nearly all amino acids, glucose, HCO_3^-, and PO_4^{3-}. May result in metabolic acidosis (proximal renal tubular acidosis). Causes include hereditary defects (eg, Wilson disease, tyrosinemia, glycogen storage disease, cystinosis), ischemia, multiple myeloma, nephrotoxins/drugs (eg, ifosfamide, cisplatin, tenofovir, expired tetracyclines), lead poisoning.
Bartter syndrome	Reabsorptive defect in thick ascending loop of Henle. Affects $Na^+/K^+/2Cl^-$ cotransporter. Results in hypokalemia and metabolic alkalosis with hypercalciuria. Presents similarly to chronic loop diuretic use. Autosomal recessive.
Gitelman syndrome	Reabsorptive defect of NaCl in DCT. Leads to hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria. Similar to using life-long thiazide diuretics. Autosomal recessive. Less severe than Bartter syndrome.
Liddle syndrome	Gain of function mutation → ↑ Na^+ reabsorption in collecting tubules (↑ activity of Na^+ channel). Results in hypertension, hypokalemia, metabolic alkalosis, ↓ aldosterone. Presents like hyperaldosteronism, but aldosterone is nearly undetectable. Autosomal dominant. Treatment: amiloride.
Syndrome of Apparent Mineralocorticoid Excess	Hereditary deficiency of 11β-hydroxysteroid dehydrogenase, which normally converts cortisol (can activate mineralocorticoid receptors) to cortisone (inactive on mineralocorticoid receptors) in cells containing mineralocorticoid receptors. Excess cortisol in these cells from enzyme deficiency → ↑ mineralocorticoid receptor activity → hypertension, hypokalemia, metabolic alkalosis. Low serum aldosterone levels. Can acquire disorder from glycyrrhetinic acid (present in licorice), which blocks activity of 11β-hydroxysteroid dehydrogenase. Treatment: corticosteroids (exogenous corticosteroids ↓ endogenous cortisol production → ↓ mineralocorticoid receptor activation). Cortisol tries to be the **SAME** as aldosterone.

Relative concentrations along proximal convoluted tubules

[TF/P] > 1
when solute is
reabsorbed less quickly
than water or when solute
is secreted

[TF/P] = 1
when solute
and water are
reabsorbed at the
same rate

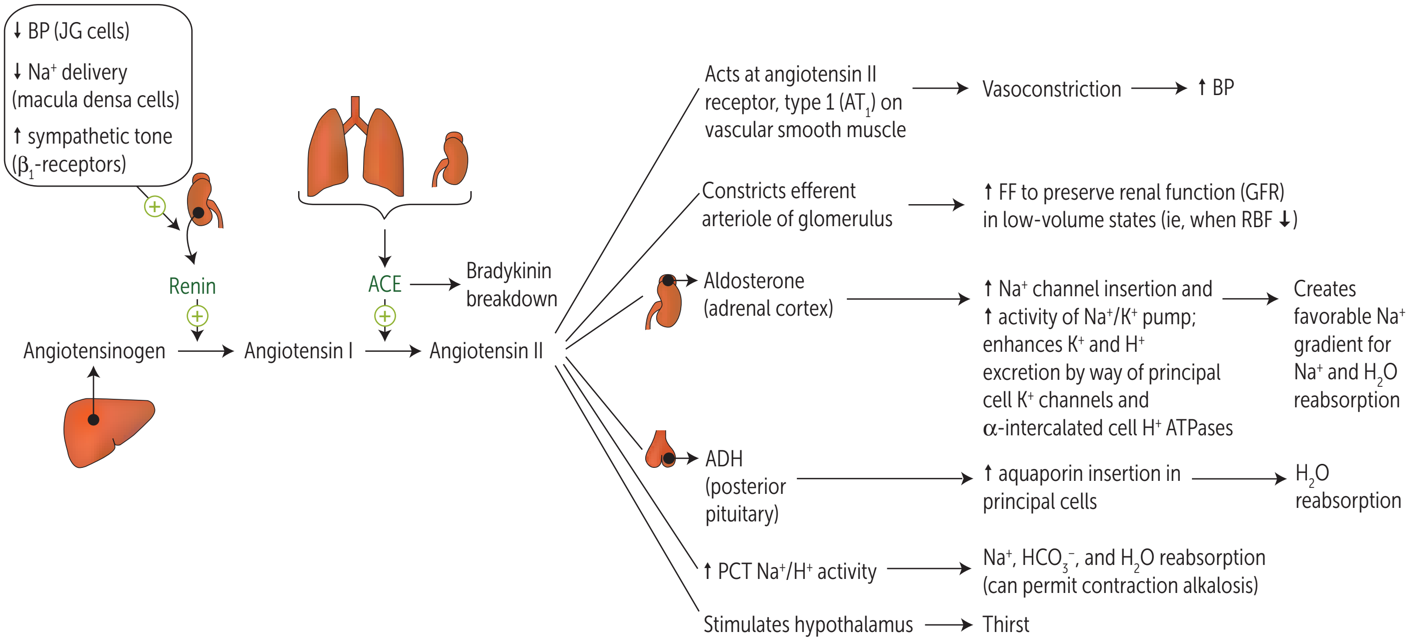
[TF/P] < 1
when solute
is reabsorbed more
quickly than water



Tubular inulin ↑ in concentration (but not amount) along the PCT as a result of water reabsorption.

Cl^- reabsorption occurs at a slower rate than Na^+ in early PCT and then matches the rate of Na^+ reabsorption more distally. Thus, its relative concentration ↑ before it plateaus.

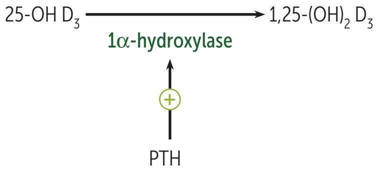
Renin-angiotensin-aldosterone system


↓ BP (JG cells)
↓ Na^+ delivery (macula densa cells)
↑ sympathetic tone (β_1-receptors)
+
Renin
+
Angiotensinogen
Angiotensin I
ACE
+
Bradykinin breakdown
Angiotensin II
Acts at angiotensin II receptor, type 1 (AT_1) on vascular smooth muscle
Vasoconstriction
↑ BP
Constricts efferent arteriole of glomerulus
↑ FF to preserve renal function (GFR) in low-volume states (ie, when RBF ↓)
Aldosterone (adrenal cortex)
↑ Na^+ channel insertion and ↑ activity of Na^+/K^+ pump; enhances K^+ and H^+ excretion by way of principal cell K^+ channels and α-intercalated cell H^+ ATPases
Creates favorable Na^+ gradient for Na^+ and H_2O reabsorption
ADH (posterior pituitary)
↑ aquaporin insertion in principal cells
H_2O reabsorption
↑ PCT Na^+/H^+ activity
Na^+, HCO_3^-, and H_2O reabsorption (can permit contraction alkalosis)
Stimulates hypothalamus
Thirst

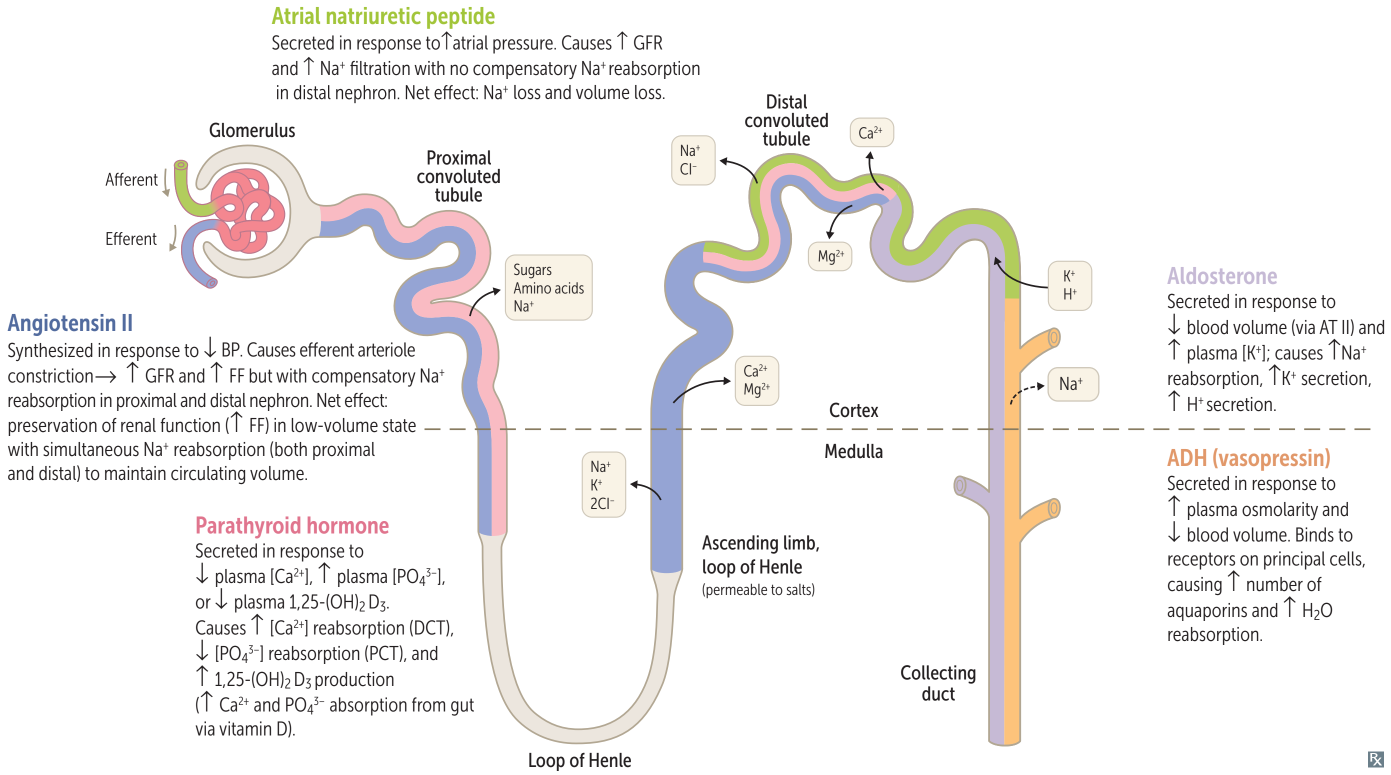
Renin	Secreted by JG cells in response to ↓ renal arterial pressure, ↑ renal sympathetic discharge (β_1 effect), and ↓ Na^+ delivery to macula densa cells.
AT II	Helps maintain blood volume and blood pressure. Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects.
ANP, BNP	Released from atria (ANP) and ventricles (BNP) in response to ↑ volume; may act as a "check" on renin-angiotensin-aldosterone system; relaxes vascular smooth muscle via cGMP → ↑ GFR, ↓ renin. Dilates afferent arteriole, constricts efferent arteriole, promotes natriuresis.
ADH	Primarily regulates osmolarity; also responds to low blood volume states.
Aldosterone	Primarily regulates ECF volume and Na^+ content; responds to low blood volume states. Responds to hyperkalemia by ↑ K^+ excretion.

Juxtaglomerular apparatus	Consists of mesangial cells, JG cells (modified smooth muscle of afferent arteriole) and the macula densa (NaCl sensor, part of DCT). JG cells secrete renin in response to ↓ renal blood pressure and ↑ sympathetic tone (β_1). Macula densa cells sense ↓ NaCl delivery to DCT → ↑ renin release → efferent arteriole vasoconstriction → ↑ GFR.	JGA maintains GFR via renin-angiotensin-aldosterone system. β-blockers can decrease BP by inhibiting β_1-receptors of the JGA → ↓ renin release.

Kidney endocrine functions

Erythropoietin	Released by interstitial cells in peritubular capillary bed in response to hypoxia.	Stimulates RBC proliferation in bone marrow. Erythropoietin often supplemented in chronic kidney disease.
Calciferol (vitamin D)	PCT cells convert 25-OH vitamin D_3 to 1,25-$(OH)_2$ vitamin D_3 (calcitriol, active form).	 25-OH D_3 1,25-$(OH)_2$ D_3 1α-hydroxylase ⊕ PTH
Prostaglandins	Paracrine secretion vasodilates the afferent arterioles to ↑ RBF.	NSAIDs block renal-protective prostaglandin synthesis → constriction of afferent arteriole and ↓ GFR; this may result in acute renal failure in low renal blood flow states.
Dopamine	Secreted by PCT cells, promotes natriuresis. At low doses, dilates interlobular arteries, afferent arterioles, efferent arterioles → ↑ RBF, little or no change in GFR. At higher doses, acts as vasoconstrictor.	

Hormones acting on kidney


Glomerulus
Afferent
Efferent
Proximal convoluted tubule
Sugars
Amino acids
Na^+
Distal convoluted tubule
Na^+
Cl^-
Ca^{2+}
Mg^{2+}
K^+
H^+
Na^+
Ca^{2+}
Mg^{2+}
Cortex
Medulla
Na^+
K^+
$2Cl^-$
Ascending limb, loop of Henle
(permeable to salts)
Collecting duct
Loop of Henle

Atrial natriuretic peptide
Secreted in response to ↑ atrial pressure. Causes ↑ GFR and ↑ Na^+ filtration with no compensatory Na^+ reabsorption in distal nephron. Net effect: Na^+ loss and volume loss.

Angiotensin II
Synthesized in response to ↓ BP. Causes efferent arteriole constriction → ↑ GFR and ↑ FF but with compensatory Na^+ reabsorption in proximal and distal nephron. Net effect: preservation of renal function (↑ FF) in low-volume state with simultaneous Na^+ reabsorption (both proximal and distal) to maintain circulating volume.

Parathyroid hormone
Secreted in response to ↓ plasma [Ca^{2+}], ↑ plasma [PO_4^{3-}], or ↓ plasma 1,25-$(OH)_2$ D_3.
Causes ↑ [Ca^{2+}] reabsorption (DCT), ↓ [PO_4^{3-}] reabsorption (PCT), and ↑ 1,25-$(OH)_2$ D_3 production (↑ Ca^{2+} and PO_4^{3-} absorption from gut via vitamin D).

Aldosterone
Secreted in response to ↓ blood volume (via AT II) and ↑ plasma [K^+]; causes ↑ Na^+ reabsorption, ↑ K^+ secretion, ↑ H^+ secretion.

ADH (vasopressin)
Secreted in response to ↑ plasma osmolarity and ↓ blood volume. Binds to receptors on principal cells, causing ↑ number of aquaporins and ↑ H_2O reabsorption.

Potassium shifts

SHIFTS K^+ INTO CELL (CAUSING HYPOKALEMIA)	SHIFTS K^+ OUT OF CELL (CAUSING HYPERKALEMIA)
	Digitalis (blocks Na^+/K^+ ATPase)
Hypo-osmolarity	Hyper**O**smolarity
	Lysis of cells (eg, crush injury, rhabdomyolysis, tumor lysis syndrome)
Alkalosis	**A**cidosis
β-adrenergic agonist (↑ Na^+/K^+ ATPase)	**β**-blocker
Insulin (↑ Na^+/K^+ ATPase)	High blood **S**ugar (insulin deficiency)
Insulin shifts K^+ **in**to cells	**S**uccinylcholine (↑ risk in burns/muscle trauma) Hyperkalemia? **DO LAβSS**

Electrolyte disturbances

ELECTROLYTE	LOW SERUM CONCENTRATION	HIGH SERUM CONCENTRATION
Na^+	Nausea and malaise, stupor, coma, seizures	Irritability, stupor, coma
K^+	U waves and flattened T waves on ECG, arrhythmias, muscle cramps, spasm, weakness	Wide QRS and peaked T waves on ECG, arrhythmias, muscle weakness
Ca^{2+}	Tetany, seizures, QT prolongation, twitching (Chvostek sign), spasm (Trousseau sign)	**Stones** (renal), **bones** (pain), **groans** (abdominal pain), **thrones** (↑ urinary frequency), **psychiatric overtones** (anxiety, altered mental status)
Mg^{2+}	Tetany, torsades de pointes, hypokalemia, hypocalcemia (when $[Mg^{2+}] < 1.2$ mg/dL)	↓ DTRs, lethargy, bradycardia, hypotension, cardiac arrest, hypocalcemia
PO_4^{3-}	Bone loss, osteomalacia (adults), rickets (children)	Renal stones, metastatic calcifications, hypocalcemia

Features of renal disorders

CONDITION	BLOOD PRESSURE	PLASMA RENIN	ALDOSTERONE	SERUM Mg^{2+}	URINE Ca^{2+}
Bartter syndrome	—	↑	↑		**↑**
Gitelman syndrome	—	↑	↑	↓	**↓**
Liddle syndrome	↑	↓	**↓**		
SIADH	—/↑	↓	↓		
Primary hyperaldosteronism (Conn syndrome)	↑	↓	**↑**		
Renin-secreting tumor	↑	**↑**	↑		

↑ ↓ = 1° disturbance.

Acid-base physiology

	pH	P_{CO_2}	$[HCO_3^-]$	COMPENSATORY RESPONSE
Metabolic acidosis	↓	↓	↓	Hyperventilation (immediate)
Metabolic alkalosis	↑	↑	↑	Hypoventilation (immediate)
Respiratory acidosis	↓	↑	↑	↑ renal $[HCO_3^-]$ reabsorption (delayed)
Respiratory alkalosis	↑	↓	↓	↓ renal $[HCO_3^-]$ reabsorption (delayed)

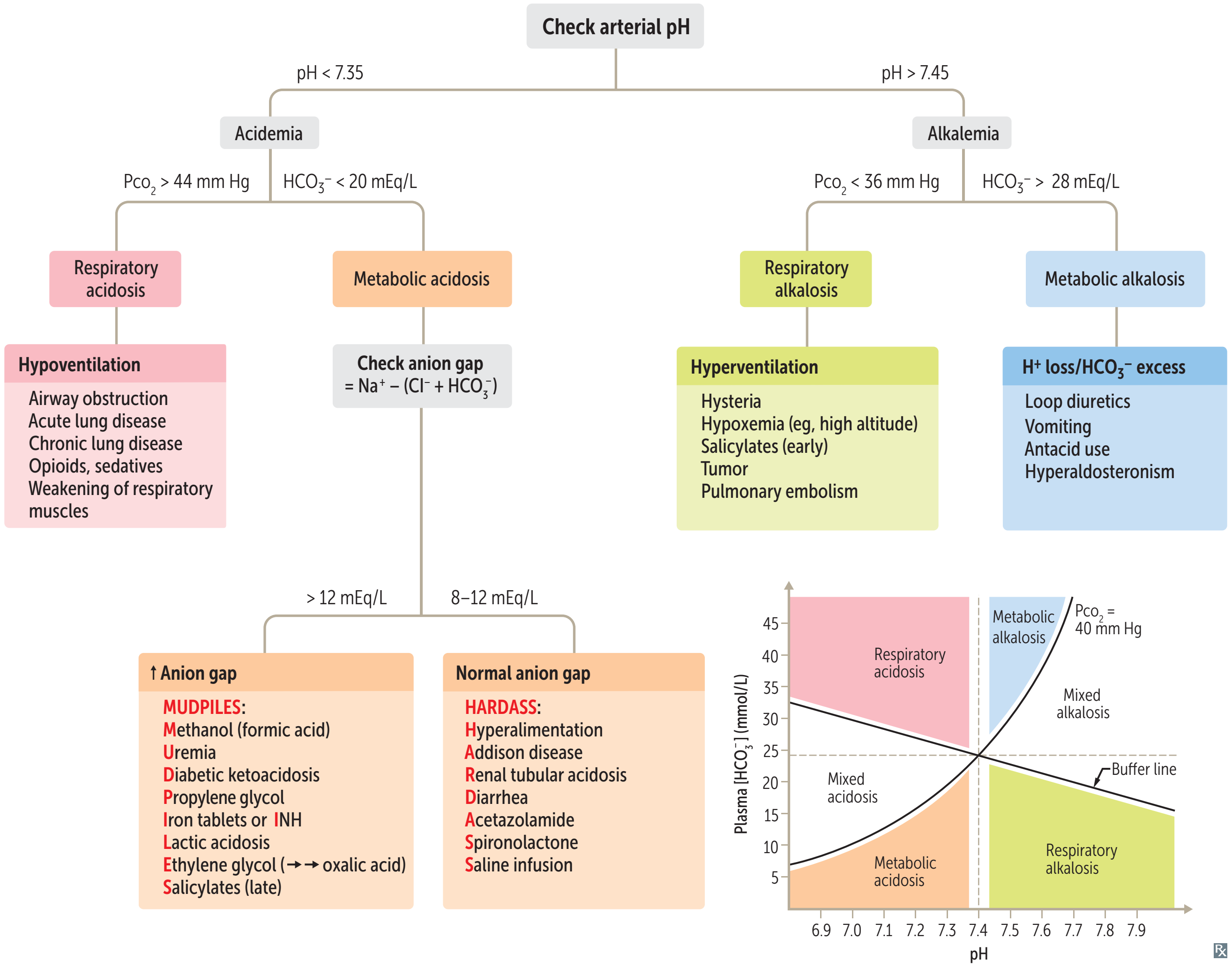
Key: ↑ ↓ = 1° disturbance; ↓ ↑ = compensatory response.

Henderson-Hasselbalch equation: $$\text{pH} = 6.1 + \log \frac{[HCO_3^-]}{0.03\ P_{CO_2}}$$

Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured P_{CO_2} > predicted P_{CO_2} → concomitant respiratory acidosis; if measured P_{CO_2} < predicted P_{CO_2} → concomitant respiratory alkalosis:

$$P_{CO_2} = 1.5\ [HCO_3^-] + 8 \pm 2$$

Acidosis and alkalosis



Check arterial pH

pH < 7.35 → **Acidemia**

- P_{CO_2} > 44 mm Hg → Respiratory acidosis
- HCO_3^- < 20 mEq/L → Metabolic acidosis

pH > 7.45 → **Alkalemia**

- P_{CO_2} < 36 mm Hg → Respiratory alkalosis
- HCO_3^- > 28 mEq/L → Metabolic alkalosis

Hypoventilation

- Airway obstruction
- Acute lung disease
- Chronic lung disease
- Opioids, sedatives
- Weakening of respiratory muscles

Metabolic acidosis → Check anion gap $= Na^+ - (Cl^- + HCO_3^-)$

> 12 mEq/L → **↑ Anion gap**

MUDPILES:

- **M**ethanol (formic acid)
- **U**remia
- **D**iabetic ketoacidosis
- **P**ropylene glycol
- **I**ron tablets or **I**NH
- **L**actic acidosis
- **E**thylene glycol (→→ oxalic acid)
- **S**alicylates (late)

8–12 mEq/L → **Normal anion gap**

HARDASS:

- **H**yperalimentation
- **A**ddison disease
- **R**enal tubular acidosis
- **D**iarrhea
- **A**cetazolamide
- **S**pironolactone
- **S**aline infusion

Hyperventilation

- Hysteria
- Hypoxemia (eg, high altitude)
- Salicylates (early)
- Tumor
- Pulmonary embolism

H^+ loss/HCO_3^- excess

- Loop diuretics
- Vomiting
- Antacid use
- Hyperaldosteronism

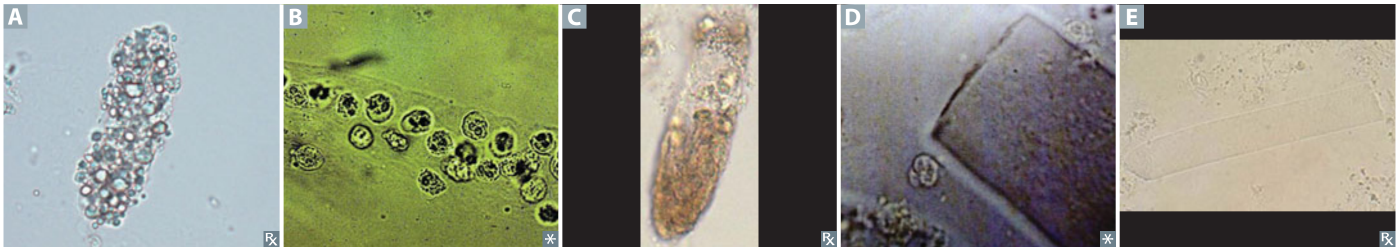
Plasma [HCO3⁻] (mmol/L)
45
40
35
30
25
20
15
10
5
pH
6.9
7.0
7.1
7.2
7.3
7.4
7.5
7.6
7.7
7.8
7.9
Respiratory acidosis
Metabolic alkalosis
Pco2 = 40 mm Hg
Mixed alkalosis
Mixed acidosis
Buffer line
Metabolic acidosis
Respiratory alkalosis

Renal tubular acidosis A disorder of the renal tubules that leads to normal anion gap (hyperchloremic) metabolic acidosis.

RTA TYPE	NOTES
Distal renal tubular acidosis (type 1)	Urine pH > 5.5. Defect in ability of α intercalated cells to secrete H^+ → no new HCO_3^- is generated → metabolic acidosis. Associated with **hypokalemia**, ↑ risk for calcium phosphate kidney stones (due to ↑ urine pH and ↑ bone turnover). Causes: amphotericin B toxicity, analgesic nephropathy, congenital anomalies (obstruction) of urinary tract.
Proximal renal tubular acidosis (type 2)	Urine pH < 5.5. Defect in PCT HCO_3^- reabsorption → ↑ excretion of HCO_3^- in urine and subsequent metabolic acidosis. Urine is acidified by α-intercalated cells in collecting tubule. Associated with **hypokalemia**, ↑ risk for hypophosphatemic rickets. Causes: Fanconi syndrome and carbonic anhydrase inhibitors.
Hyperkalemic renal tubular acidosis (type 4)	Urine pH < 5.5. Hypoaldosteronism → **hyperkalemia** → ↓ NH_3 synthesis in PCT → ↓ NH_4^+ excretion. Causes: ↓ aldosterone production (eg, diabetic hyporeninism, ACE inhibitors, ARBs, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (eg, K^+-sparing diuretics, nephropathy due to obstruction, TMP/SMX).

▸ RENAL—PATHOLOGY

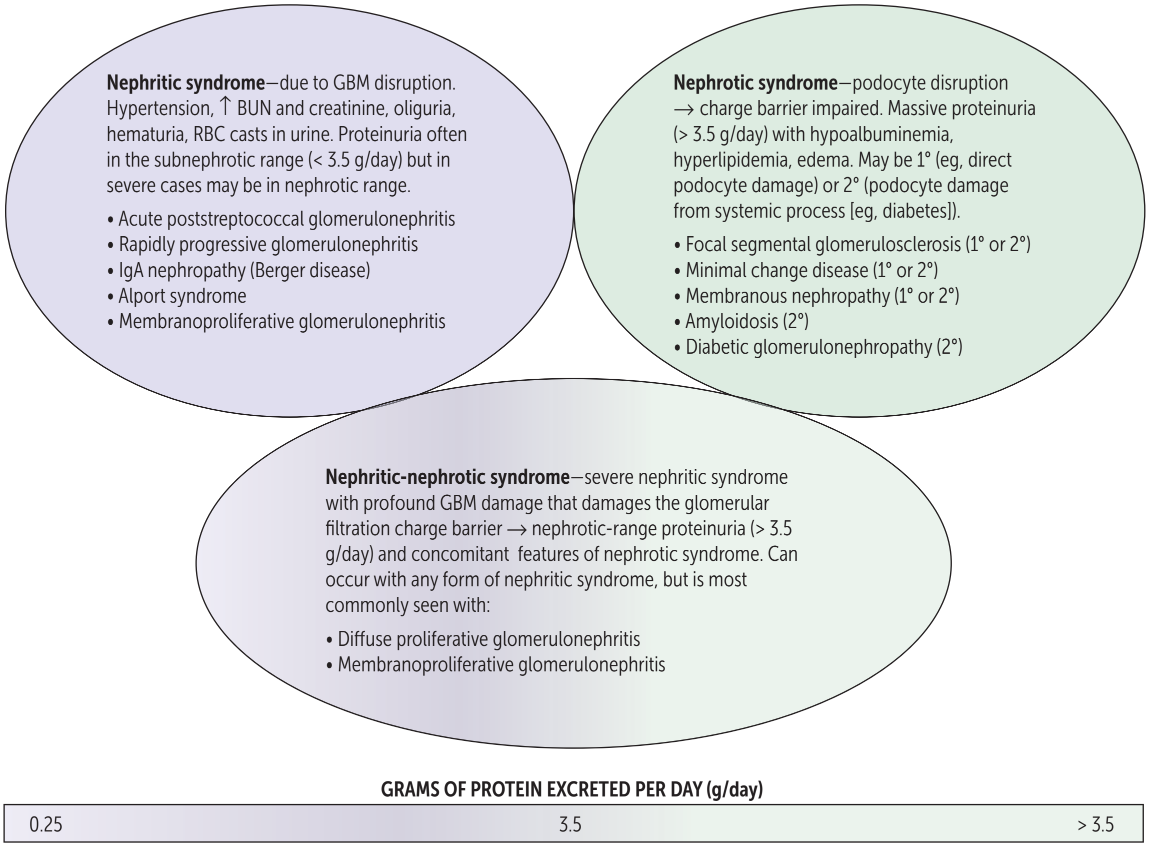
Casts in urine	Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin. Bladder cancer, kidney stones → hematuria, no casts. Acute cystitis → pyuria, no casts.
RBC casts A	Glomerulonephritis, malignant hypertension.
WBC casts B	Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.
Fatty casts ("oval fat bodies")	Nephrotic syndrome. Associated with "Maltese cross" sign.
Granular ("muddy brown") casts C	Acute tubular necrosis.
Waxy casts D	End-stage renal disease/chronic renal failure.
Hyaline casts E	Nonspecific, can be a normal finding, often seen in concentrated urine samples.



Nomenclature of glomerular disorders

TYPE	CHARACTERISTICS	EXAMPLE
Focal	< 50% of glomeruli are involved	Focal segmental glomerulosclerosis
Diffuse	> 50% of glomeruli are involved	Diffuse proliferative glomerulonephritis
Proliferative	Hypercellular glomeruli	Membranoproliferative glomerulonephritis
Membranous	Thickening of glomerular basement membrane (GBM)	Membranous nephropathy
Primary glomerular disease	1° disease of the kidney specifically impacting the glomeruli	Minimal change disease
Secondary glomerular disease	Systemic disease or disease of another organ system that also impacts the glomeruli	SLE, diabetic nephropathy

Glomerular diseases



Nephritic syndrome—due to GBM disruption. Hypertension, ↑ BUN and creatinine, oliguria, hematuria, RBC casts in urine. Proteinuria often in the subnephrotic range (< 3.5 g/day) but in severe cases may be in nephrotic range.

- Acute poststreptococcal glomerulonephritis
- Rapidly progressive glomerulonephritis
- IgA nephropathy (Berger disease)
- Alport syndrome
- Membranoproliferative glomerulonephritis

Nephrotic syndrome—podocyte disruption → charge barrier impaired. Massive proteinuria (> 3.5 g/day) with hypoalbuminemia, hyperlipidemia, edema. May be 1° (eg, direct podocyte damage) or 2° (podocyte damage from systemic process [eg, diabetes]).

- Focal segmental glomerulosclerosis (1° or 2°)
- Minimal change disease (1° or 2°)
- Membranous nephropathy (1° or 2°)
- Amyloidosis (2°)
- Diabetic glomerulonephropathy (2°)

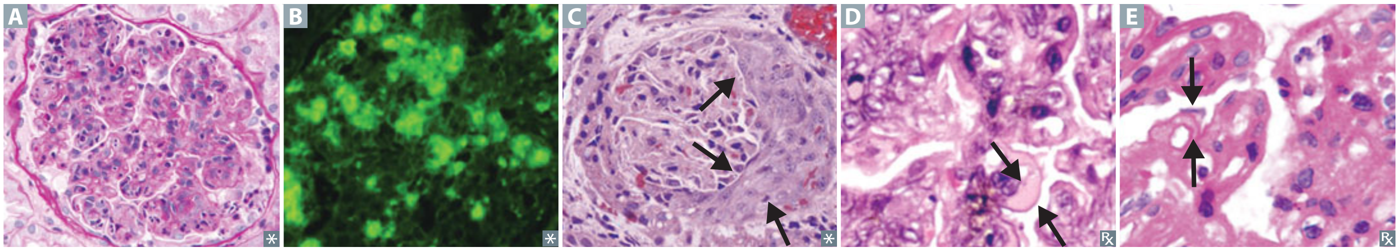
Nephritic-nephrotic syndrome—severe nephritic syndrome with profound GBM damage that damages the glomerular filtration charge barrier → nephrotic-range proteinuria (> 3.5 g/day) and concomitant features of nephrotic syndrome. Can occur with any form of nephritic syndrome, but is most commonly seen with:

- Diffuse proliferative glomerulonephritis
- Membranoproliferative glomerulonephritis

Nephritic syndrome	NephrItic syndrome = Inflammatory process. When glomeruli are involved, leads to hematuria and RBC casts in urine. Associated with azotemia, oliguria, hypertension (due to salt retention), proteinuria.	
Acute poststreptococcal glomerulonephritis	LM—glomeruli enlarged and hypercellular A. IF—("starry sky") granular appearance ("lumpy-bumpy") B due to IgG, IgM, and C3 deposition along GBM and mesangium. EM—subepithelial immune complex (IC) humps.	Most frequently seen in children. Occurs ~ 2–4 weeks after group A streptococcal infection of pharynx or skin. Resolves spontaneously. Type III hypersensitivity reaction. Presents with peripheral and periorbital edema, cola-colored urine, hypertension. Positive strep titers/serologies, ↓ complement levels (C3) due to consumption.
Rapidly progressive (crescentic) glomerulonephritis	LM and IF—crescent moon shape C. Crescents consist of fibrin and plasma proteins (eg, C3b) with glomerular parietal cells, monocytes, macrophages. Several disease processes may result in this pattern, in particular:	Poor prognosis. Rapidly deteriorating renal function (days to weeks).
	▪ **Goodpasture syndrome**—type II hypersensitivity reaction; antibodies to GBM and alveolar basement membrane → linear IF	Hematuria/hemoptysis. Treatment: emergent plasmapheresis.
	▪ Granulomatosis with polyangiitis (Wegener)	PR3-ANCA/c-ANCA. Pauci-immune (no Ig/C3 deposition).
	▪ Microscopic Polyangiitis	MPO-ANCA/p-ANCA. Pauci-immune (no Ig/C3 deposition).
Diffuse proliferative glomerulonephritis	Often due to SLE or membranoproliferative glomerulonephritis. LM—"wire looping" of capillaries. EM—subendothelial and sometimes intramembranous IgG-based ICs often with C3 deposition. IF—granular.	A common cause of death in SLE (think "wire lupus"). DPGN and MPGN often present as nephrotic syndrome and nephritic syndrome concurrently.
IgA nephropathy (Berger disease)	LM—mesangial proliferation. EM—mesangial IC deposits. IF—IgA-based IC deposits in mesangium. Renal pathology of Henoch-Schönlein purpura.	Episodic gross hematuria that occurs concurrently with respiratory or GI tract infections (IgA is secreted by mucosal linings). Not to be confused with Buerger disease (thromboangiitis obliterans).

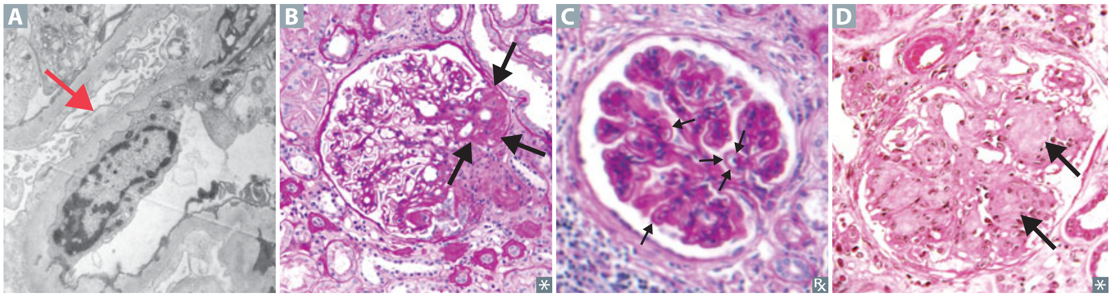
Nephritic syndrome *(continued)*

Alport syndrome	Mutation in type IV collagen → thinning and splitting of glomerular basement membrane. Most commonly X-linked dominant.	Eye problems (eg, retinopathy, lens dislocation), glomerulonephritis, sensorineural deafness; "can't see, can't pee, can't hear a bee." "Basket-weave" appearance on EM.
Membrano-proliferative glomerulonephritis	Type I—subendothelial immune complex (IC) deposits with granular IF; "tram-track" appearance on PAS stain D and H&E stain E due to GBM splitting caused by mesangial ingrowth. Type II—also called dense deposit disease.	MPGN is a nephritic syndrome that often copresents with nephrotic syndrome. Type I may be 2° to hepatitis B or C infection. May also be idiopathic. Type II is associated with C3 nephritic factor (IgG antibody that stabilizes C3 convertase → persistent complement activation → ↓ C3 levels).



LM = light microscopy; EM = electron microscopy; IF = immunofluorescence.

Nephrotic syndrome	NephrOtic syndrome—massive prOteinuria (> 3.5 g/day) with hypoalbuminemia, resulting edema, hyperlipidemia. Frothy urine with fatty casts. Due to podocyte damage disrupting glomerular filtration charge barrier. May be 1° (eg, direct sclerosis of podocytes) or 2° (systemic process [eg, diabetes] secondarily damages podocytes). Associated with hypercoagulable state (eg, thromboembolism) due to antithrombin (AT) III loss in urine and ↑ risk of infection (due to loss of immunoglobulins in urine and soft tissue compromise by edema). Severe nephritic syndrome may present with nephrotic syndrome features (nephritic-nephrotic syndrome) if damage to GBM is severe enough to damage charge barrier.	
Minimal change disease (lipoid nephrosis)	LM—normal glomeruli (lipid may be seen in PCT cells). IF ⊖. EM—effacement of foot processes A.	Most common cause of nephrotic syndrome in children. Often 1° (idiopathic) and may be triggered by recent infection, immunization, immune stimulus. Rarely, may be 2° to lymphoma (eg, cytokine-mediated damage). 1° disease has excellent response to corticosteroids.
Focal segmental glomerulosclerosis	LM—segmental sclerosis and hyalinosis B. IF—often ⊖, but may be ⊕ for nonspecific focal deposits of IgM, C3, C1. EM—effacement of foot process similar to minimal change disease.	Most common cause of nephrotic syndrome in African Americans and Hispanics. Can be 1° (idiopathic) or 2° to other conditions (eg, HIV infection, sickle cell disease, heroin abuse, massive obesity, interferon treatment, chronic kidney disease due to congenital malformations). 1° disease has inconsistent response to steroids. May progress to chronic renal disease.
Membranous nephropathy (membranous glomerulonephritis)	LM—diffuse capillary and GBM thickening C. IF—granular as a result of immune complex deposition. Nephrotic presentation of SLE. EM—"spike and dome" appearance with subepithelial deposits.	Most common cause of 1° nephrotic syndrome in Caucasian adults. Can be 1° (eg, antibodies to phospholipase A_2 receptor) or 2° to drugs (eg, NSAIDs, penicillamine, gold), infections (eg, HBV, HCV, syphilis), SLE, or solid tumors. 1° disease has poor response to steroids. May progress to chronic renal disease.
Amyloidosis	LM—Congo red stain shows apple-green birefringence under polarized light due to amyloid deposition in the mesangium.	Kidney is the most commonly involved organ (systemic amyloidosis). Associated with chronic conditions that predispose to amyloid deposition (eg, AL amyloid, AA amyloid).
Diabetic glomerulonephropathy	LM—mesangial expansion, GBM thickening, eosinophilic nodular glomerulosclerosis (Kimmelstiel-Wilson lesions, arrows in D).	Nonenzymatic glycosylation of GBM → ↑ permeability, thickening. Nonenzymatic glycosylation of efferent arterioles (hyaline arteriosclerosis) → ↑ GFR → mesangial expansion. Most common cause of end-stage renal disease in the United States.

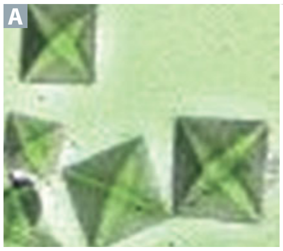


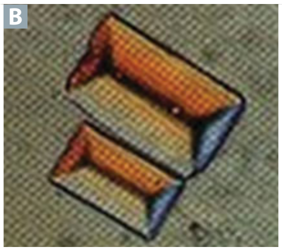
Kidney stones

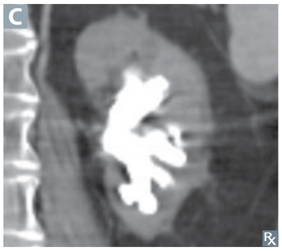
Can lead to severe complications such as hydronephrosis, pyelonephritis. Presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake.

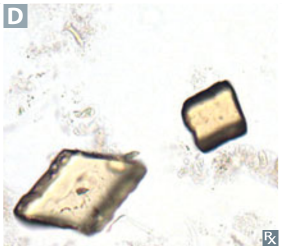
Most common kidney stone presentation: calcium oxalate stone in patient with hypercalciuria and normocalcemia.

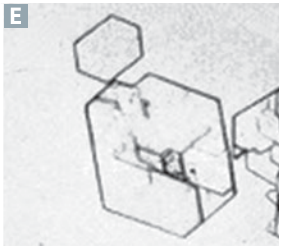
CONTENT	PRECIPITATES WITH	X-RAY FINDINGS	CT FINDINGS	URINE CRYSTAL	NOTES
Calcium	Calcium oxalate: hypocitraturia	Radiopaque	Radiopaque	Shaped like envelope A or dumbbell	Calcium stones most common (80%); calcium oxalate more common than calcium phosphate stones. Hypocitraturia often associated with ↓ urine pH. Can result from ethylene glycol (antifreeze) ingestion, vitamin C abuse, hypocitraturia, malabsorption (eg, Crohn disease). Treatment: thiazides, citrate, low-sodium diet.
	Calcium phosphate: ↑ pH	Radiopaque	Radiopaque	Wedge-shaped prism	Treatment: low-sodium diet, thiazides.
Ammonium magnesium phosphate	↑ pH	Radiopaque	Radiopaque	Coffin lid B	Also known as struvite; account for 15% of stones. Caused by infection with urease ⊕ bugs (eg, *Proteus mirabilis*, *Staphylococcus saprophyticus*, *Klebsiella*) that hydrolyze urea to ammonia → urine alkalinization. Commonly form staghorn calculi C. Treatment: eradication of underlying infection, surgical removal of stone.
Uric acid	↓ pH	RadiolUcent	Minimally visible	Rhomboid D or rosettes	About 5% of all stones. Risk factors: ↓ urine volume, arid climates, acidic pH. Strong association with hyperuricemia (eg, gout). Often seen in diseases with ↑ cell turnover (eg, leukemia). Treatment: alkalinization of urine, allopurinol.
Cystine	↓ pH	Radiolucent	Sometimes visible	Hexagonal E	Hereditary (autosomal recessive) condition in which Cystine-reabsorbing PCT transporter loses function, causing cystinuria. Transporter defect also results in poor reabsorption of Ornithine, Lysine, Arginine (COLA). Cystine is poorly soluble, thus stones form in urine. Usually begins in childhood. Can form staghorn calculi. Sodium cyanide nitroprusside test ⊕. "SIXtine" stones have SIX sides. Treatment: low sodium diet, alkalinization of urine, chelating agents if refractory.



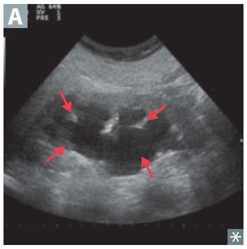








Hydronephrosis



Distention/dilation of renal pelvis and calyces A. Usually caused by urinary tract obstruction (eg, renal stones, severe BPH, cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilation occurs proximal to site of pathology. Serum creatinine becomes elevated if obstruction is bilateral or if patient has only one kidney. Leads to compression and possible atrophy of renal cortex and medulla.

Renal cell carcinoma

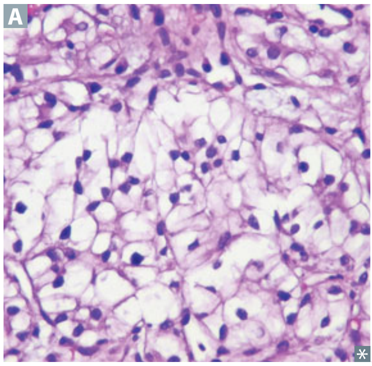
Originates from PCT cells → polygonal clear cells A filled with accumulated lipids and carbohydrates. Often golden-yellow B due to ↑ lipid content. Most common in men 50–70 years old. ↑ incidence with smoking and obesity. Manifests clinically with hematuria, palpable mass, 2° polycythemia, flank pain, fever, weight loss. Invades renal vein (may develop varicocele if left sided) then IVC and spreads hematogenously; metastasizes to lung and bone.

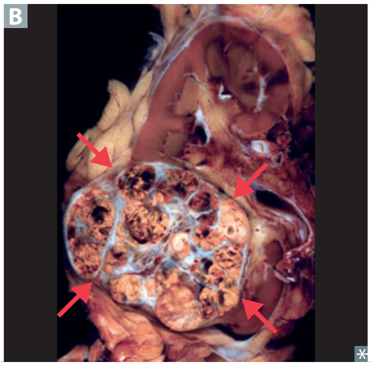
Treatment: surgery/ablation for localized disease. Immunotherapy (eg, aldesleukin) or targeted therapy for metastatic disease, rarely curative. Resistant to chemotherapy and radiation therapy.

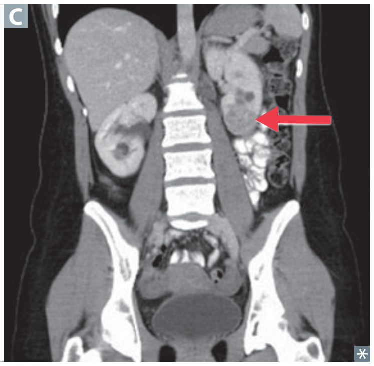
Most common 1° renal malignancy C.

Associated with gene deletion on chromosome 3 (sporadic or inherited as von Hippel-Lindau syndrome). RCC = 3 letters = chromosome 3.

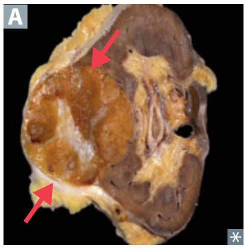
Associated with paraneoplastic syndromes (eg, ectopic EPO, ACTH, PTHrP, renin).







Renal oncocytoma

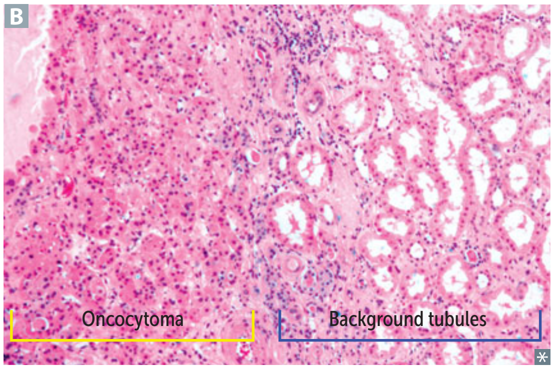


Benign epithelial cell tumor arising from collecting ducts (arrows in A point to well-circumscribed mass with central scar).

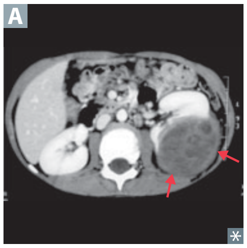
Large eosinophilic cells with abundant mitochondria without perinuclear clearing B (vs chromophobe renal cell carcinoma).

Presents with painless hematuria, flank pain, abdominal mass.

Often resected to exclude malignancy (eg, renal cell carcinoma).



Nephroblastoma (Wilms tumor)



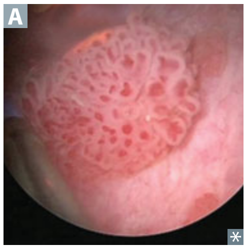
Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Presents with large, palpable, unilateral flank mass A and/or hematuria.

"Loss of function" mutations of tumor suppressor genes *WT1* or *WT2* on chromosome 11.

May be a part of several syndromes:

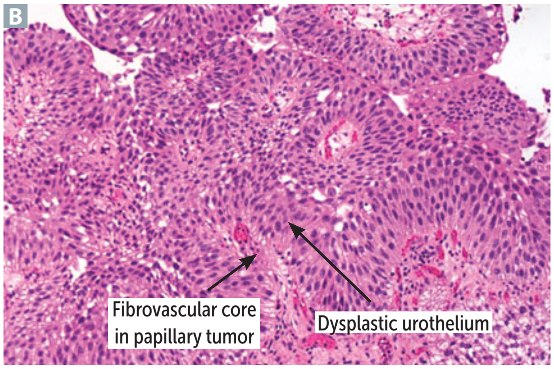
- **WAGR** complex: **W**ilms tumor, **A**niridia (absence of iris), **G**enitourinary malformations, mental **R**etardation/intellectual disability (*WT1* deletion)
- Denys-Drash: Wilms tumor, early-onset nephrotic syndrome, male pseudohermaphroditism (*WT1* mutation)
- Beckwith-Wiedemann: Wilms tumor, macroglossia, organomegaly, hemihyperplasia (*WT2* mutation)

Transitional cell carcinoma



Most common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder) A B. Can be suggested by painless hematuria (no casts).

Associated with problems in your **P**ee **SAC**: **P**henacetin, **S**moking, **A**niline dyes, and **C**yclophosphamide.



Squamous cell carcinoma of the bladder

Chronic irritation of urinary bladder → squamous metaplasia → dysplasia and squamous cell carcinoma.

Risk factors include *Schistosoma haematobium* infection (Middle East), chronic cystitis, smoking, chronic nephrolithiasis. Presents with painless hematuria.

Urinary incontinence

Stress incontinence	Outlet incompetence (urethral hypermobility or intrinsic sphincteric deficiency) → leak with ↑ intra-abdominal pressure (eg, sneezing, lifting). ↑ risk with obesity, vaginal delivery, prostate surgery. ⊕ bladder stress test (directly observed leakage from urethra upon coughing or Valsalva maneuver). Treatment: pelvic floor muscle strengthening (Kegel) exercises, weight loss, pessaries.
Urgency incontinence	Overactive bladder (detrusor instability) → leak with urge to void immediately. Treatment: Kegel exercises, bladder training (timed voiding, distraction or relaxation techniques), antimuscarinics (eg, oxybutynin).
Mixed incontinence	Features of both stress and urgency incontinence.
Overflow incontinence	Incomplete emptying (detrusor underactivity or outlet obstruction) → leak with overfilling. ↑ post-void residual (urinary retention) on catheterization or ultrasound. Treatment: catheterization, relieve obstruction (eg, α-blockers for BPH).

Urinary tract infection (acute bacterial cystitis)

Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency. Systemic signs (eg, high fever, chills) are usually absent.

Risk factors include female gender (short urethra), sexual intercourse ("honeymoon cystitis"), indwelling catheter, diabetes mellitus, impaired bladder emptying.

Causes:

- *E coli* (most common).
- *Staphylococcus saprophyticus*—seen in sexually active young women (*E coli* is still more common in this group).
- *Klebsiella*.
- *Proteus mirabilis*—urine has ammonia scent.

Lab findings: ⊕ leukocyte esterase. ⊕ nitrites (indicate gram ⊖ organisms). Sterile pyuria and ⊖ urine cultures suggest urethritis by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.

Pyelonephritis

Acute pyelonephritis

Neutrophils infiltrate renal interstitium A. Affects cortex with relative sparing of glomeruli/vessels. Presents with fevers, flank pain (costovertebral angle tenderness), nausea/vomiting, chills.

Causes include ascending UTI (*E coli* is most common), hematogenous spread to kidney. Presents with WBCs in urine +/– WBC casts. CT would show striated parenchymal enhancement B.

Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy.

Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess, urosepsis.

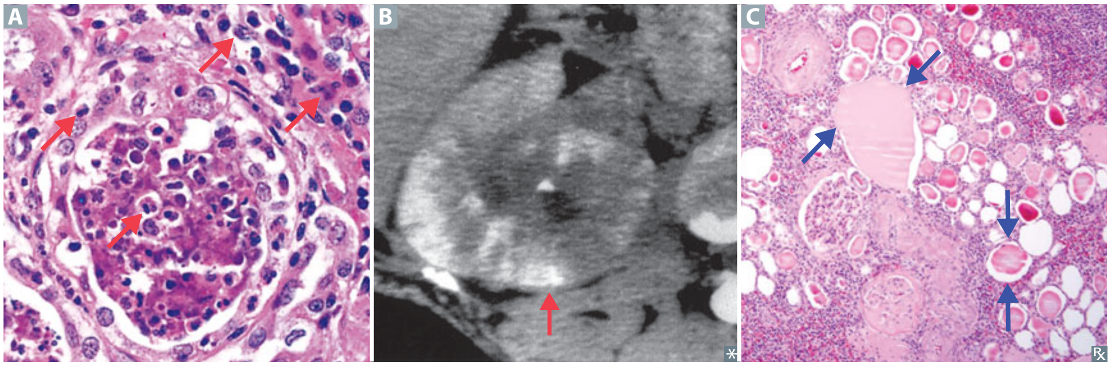
Treatment: antibiotics.

Chronic pyelonephritis

The result of recurrent episodes of acute pyelonephritis. Typically requires predisposition to infection such as vesicoureteral reflux or chronically obstructing kidney stones.

Coarse, asymmetric corticomedullary scarring, blunted calyx. Tubules can contain eosinophilic casts resembling thyroid tissue C (thyroidization of kidney).

Xanthogranulomatous pyelonephritis—rare; grossly orange nodules that can mimic tumor nodules; characterized by widespread kidney damage due to granulomatous tissue containing foamy macrophages.



Diffuse cortical necrosis

Acute generalized cortical infarction of both kidneys. Likely due to a combination of vasospasm and DIC.

Associated with obstetric catastrophes (eg, abruptio placentae), septic shock.

Renal osteodystrophy	Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic renal disease → 2° hyperparathyroidism. Hyperphosphatemia also independently ↓ serum Ca^{2+} by causing tissue calcifications, whereas ↓ 1,25-$(OH)_2$ D_3 → ↓ intestinal Ca^{2+} absorption. Causes subperiosteal thinning of bones.

Acute kidney injury (acute renal failure)	Acute kidney injury is defined as an abrupt decline in renal function as measured by ↑ creatinine and ↑ BUN or by oliguria/anuria.
Prerenal azotemia	Due to ↓ RBF (eg, hypotension) → ↓ GFR. Na^+/H_2O and BUN retained by kidney in an attempt to conserve volume → ↑ BUN/creatinine ratio (BUN is reabsorbed, creatinine is not) and ↓ FE_{Na}.
Intrinsic renal failure	Generally due to acute tubular necrosis or ischemia/toxins; less commonly due to acute glomerulonephritis (eg, RPGN, hemolytic uremic syndrome) or acute interstitial nephritis. In ATN, patchy necrosis → debris obstructing tubule and fluid backflow across necrotic tubule → ↓ GFR. Urine has epithelial/granular casts. BUN reabsorption is impaired → ↓ BUN/creatinine ratio and ↑ FE_{Na}.
Postrenal azotemia	Due to outflow obstruction (stones, BPH, neoplasia, congenital anomalies). Develops only with bilateral obstruction.

	Prerenal	Intrinsic renal	Postrenal
Urine osmolality (mOsm/kg)	> 500	< 350	< 350
Urine Na^+ (mEq/L)	< 20	> 40	> 40
FE_{Na}	< 1%	> 2%	< 1% (mild) > 2% (severe)
Serum BUN/Cr	> 20	< 15	Varies

Consequences of renal failure

Inability to make urine and excrete nitrogenous wastes.

Consequences (**MAD HUNGER**):

- **M**etabolic **A**cidosis
- **D**yslipidemia (especially ↑ triglycerides)
- **H**yperkalemia
- **U**remia—clinical syndrome marked by ↑ BUN:
  - Nausea and anorexia
  - Pericarditis
  - Asterixis
  - Encephalopathy
  - Platelet dysfunction
- **N**a^+/H_2O retention (HF, pulmonary edema, hypertension)
- **G**rowth retardation and developmental delay
- **E**rythropoietin failure (anemia)
- **R**enal osteodystrophy

2 forms of renal failure: acute (eg, ATN) and chronic (eg, hypertension, diabetes mellitus, congenital anomalies).

Acute interstitial nephritis (tubulointerstitial nephritis)

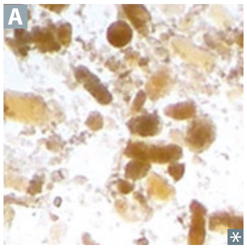
Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptens, inducing hypersensitivity (eg, diuretics, penicillin derivatives, proton pump inhibitors, sulfonamides, rifampin, NSAIDs). Less commonly may be 2° to other processes such as systemic infections (eg, mycoplasma) or autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis).

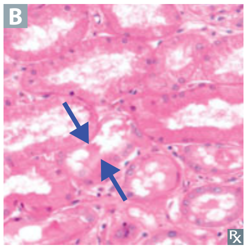
Associated with fever, rash, hematuria, and costovertebral angle tenderness, but can be asymptomatic.

Remember these **P's**:

- **P**ee (diuretics)
- **P**ain-free (NSAIDs)
- **P**enicillins and cephalosporins
- **P**roton pump inhibitors
- Rifam**P**in

Acute tubular necrosis





Most common cause of acute kidney injury in hospitalized patients. Spontaneously resolves in many cases. Can be fatal, especially during initial oliguric phase. ↑ FENa.

Key finding: granular ("muddy brown") casts A.

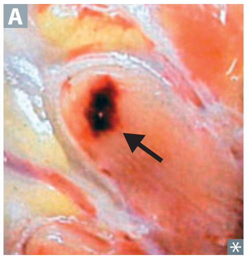
3 stages:

1. Inciting event
2. Maintenance phase—oliguric; lasts 1–3 weeks; risk of hyperkalemia, metabolic acidosis, uremia
3. Recovery phase—polyuric; BUN and serum creatinine fall; risk of hypokalemia

Can be caused by ischemic or nephrotoxic injury:

- Ischemic—2° to ↓ renal blood flow (eg, hypotension, shock, sepsis, hemorrhage, HF). Results in death of tubular cells that may slough into tubular lumen B (PCT and thick ascending limb are highly susceptible to injury).
- Nephrotoxic—2° to injury resulting from toxic substances (eg, aminoglycosides, radiocontrast agents, lead, cisplatin, ethylene glycol), crush injury (myoglobinuria), hemoglobinuria. PCT is particularly susceptible to injury.

Renal papillary necrosis

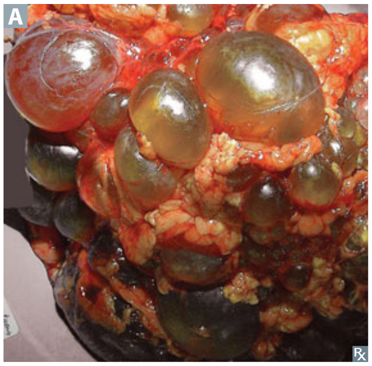


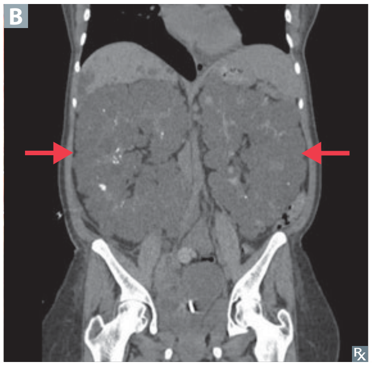
Sloughing of necrotic renal papillae A → gross hematuria and proteinuria. May be triggered by recent infection or immune stimulus. Associated with sickle cell disease or trait, acute pyelonephritis, NSAIDs, diabetes mellitus.

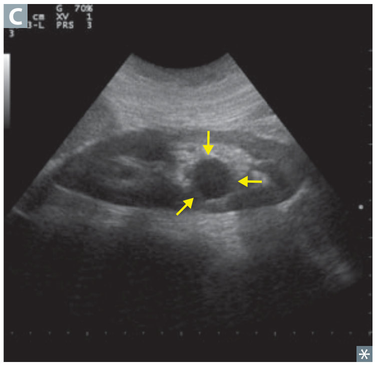
SAAD papa with **pap**illary necrosis:
Sickle cell disease or trait
Acute pyelonephritis
Analgesics (NSAIDs)
Diabetes mellitus

Renal cyst disorders

Autosomal dominant polycystic kidney disease	Numerous cysts in cortex and medulla A causing bilateral enlarged kidneys ultimately destroy kidney parenchyma. Presents with flank pain, hematuria, hypertension, urinary infection, progressive renal failure in ~ 50% of individuals. Mutation in *PKD1* (85% of cases, chromosome 16) or *PKD2* (15% of cases, chromosome 4). Death from complications of chronic kidney disease or hypertension (caused by ↑ renin production). Associated with berry aneurysms, mitral valve prolapse, benign hepatic cysts, diverticulosis. Treatment: ACE inhibitors or ARBs.
Autosomal recessive polycystic kidney disease	Cystic dilation of collecting ducts B. Often presents in infancy. Associated with congenital hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.
Medullary cystic disease	Inherited disease causing tubulointerstitial fibrosis and progressive renal insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; shrunken kidneys on ultrasound. Poor prognosis.
Simple vs complex renal cysts	Simple cysts are filled with ultrafiltrate (anechoic on ultrasound C). Very common and account for majority of all renal masses. Found incidentally and typically asymptomatic. Complex cysts, including those that are septated, enhanced, or have solid components on imaging require follow-up or removal due to risk of renal cell carcinoma.

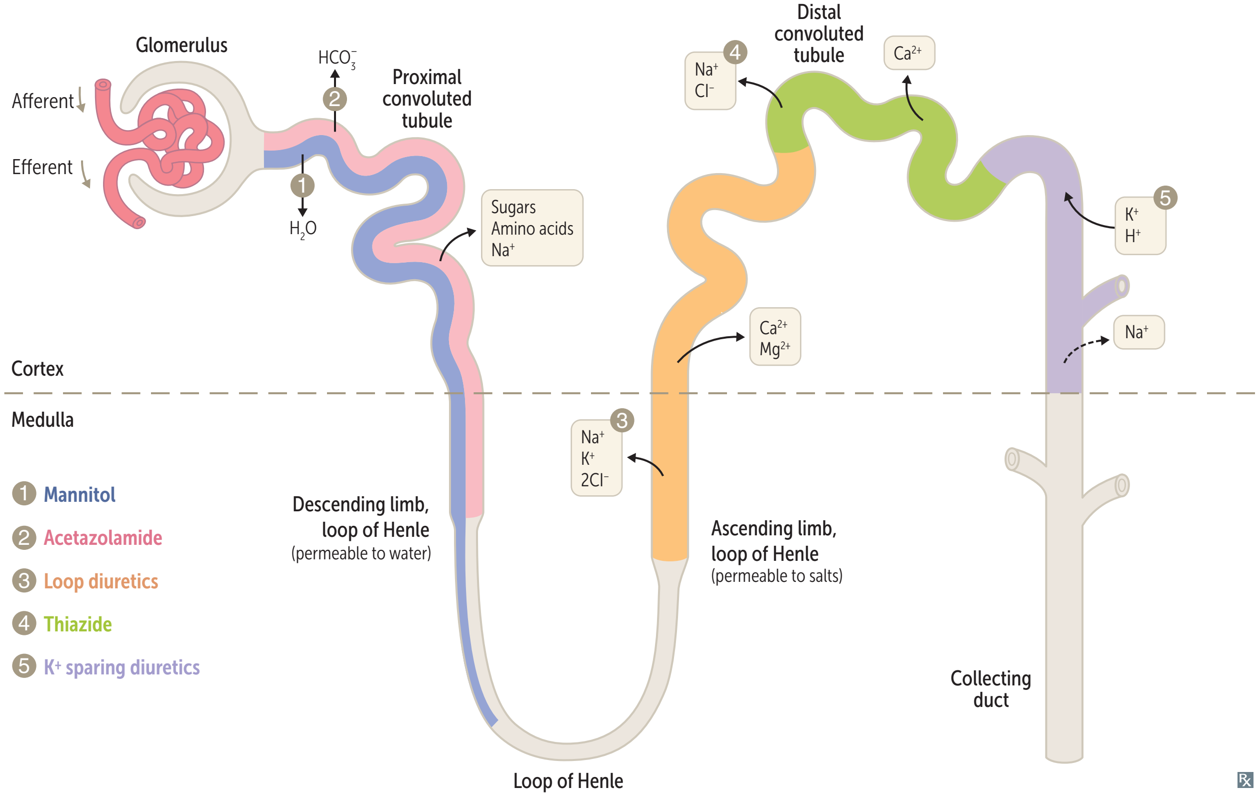






▸ RENAL—PHARMACOLOGY

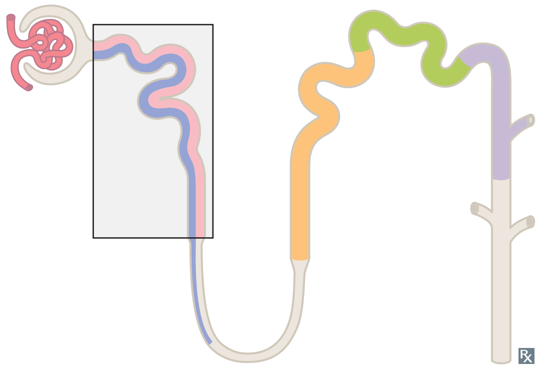
Diuretics site of action


Glomerulus
Afferent
Efferent
HCO_3^-
②
①
H_2O
Proximal convoluted tubule
Sugars
Amino acids
Na^+
Distal convoluted tubule
④
Na^+
Cl^-
Ca^{2+}
Ca^{2+}
Mg^{2+}
⑤
K^+
H^+
Na^+
Cortex
Medulla
③
Na^+
K^+
$2Cl^-$
Descending limb, loop of Henle (permeable to water)
Ascending limb, loop of Henle (permeable to salts)
Collecting duct
Loop of Henle
① Mannitol
② Acetazolamide
③ Loop diuretics
④ Thiazide
⑤ K⁺ sparing diuretics

Mannitol

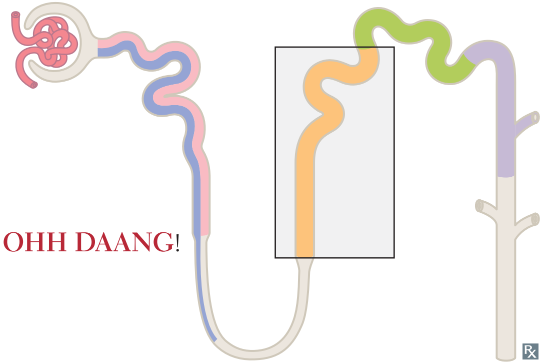
MECHANISM	Osmotic diuretic. ↑ tubular fluid osmolarity → ↑ urine flow, ↓ intracranial/intraocular pressure.
CLINICAL USE	Drug overdose, elevated intracranial/intraocular pressure.
ADVERSE EFFECTS	Pulmonary edema, dehydration. Contraindicated in anuria, HF.

Acetazolamide

MECHANISM	Carbonic anhydrase inhibitor. Causes self-limited NaHCO$_3$ diuresis and ↓ total body HCO$_3^-$ stores.	
CLINICAL USE	Glaucoma, urinary alkalinization, metabolic alkalosis, altitude sickness, pseudotumor cerebri.	
ADVERSE EFFECTS	Proximal renal tubular acidosis, paresthesias, NH$_3$ toxicity, sulfa allergy, hypokalemia.	"**ACID**"azolamide causes **ACID**osis.

Loop diuretics

Furosemide, bumetanide, torsemide

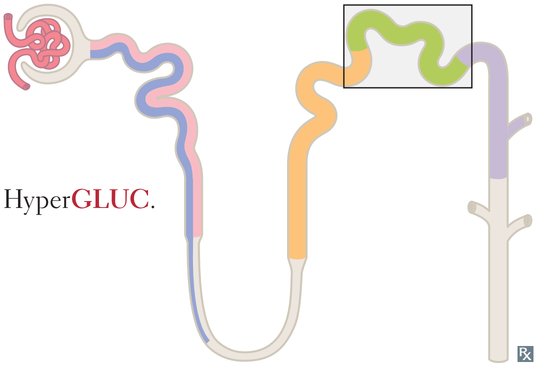
MECHANISM	Sulfonamide loop diuretics. Inhibit cotransport system (Na$^+$/K$^+$/2Cl$^-$) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Stimulate PGE release (vasodilatory effect on afferent arteriole); inhibited by NSAIDs. ↑ Ca^{2+} excretion. **L**oops **L**ose Ca^{2+}.	
CLINICAL USE	Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.	
ADVERSE EFFECTS	**O**totoxicity, **H**ypokalemia, **H**ypomagnesemia, **D**ehydration, **A**llergy (sulfa), metabolic **A**lkalosis, **N**ephritis (interstitial), **G**out.	**OHH DAANG**!

Ethacrynic acid

MECHANISM	Nonsulfonamide inhibitor of cotransport system (Na$^+$/K$^+$/2Cl$^-$) of thick ascending limb of loop of Henle.	
CLINICAL USE	Diuresis in patients allergic to sulfa drugs.	
ADVERSE EFFECTS	Similar to furosemide, but more ototoxic.	**Loop** earrings hurt your **ears**.

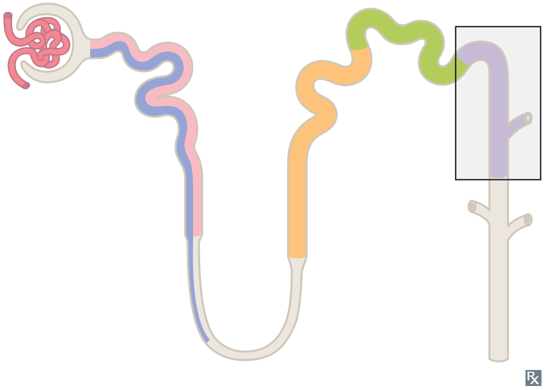
Thiazide diuretics	Hydrochlorothiazide, chlorthalidone, metolazone.
MECHANISM	Inhibit NaCl reabsorption in early DCT → ↓ diluting capacity of nephron. ↓ Ca^{2+} excretion.
CLINICAL USE	Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis.
ADVERSE EFFECTS	Hypokalemic metabolic alkalosis, hyponatremia, hyper**G**lycemia, hyper**L**ipidemia, hyper**U**ricemia, hyper**C**alcemia. Sulfa allergy.

Hyper**GLUC**.



Potassium-sparing diuretics	**S**pironolactone and eplerenone; **T**riamterene, and **A**miloride.
MECHANISM	Spironolact**one** and epleren**one** are competitive aldoster**one** receptor antagonists in cortical collecting tubule. Triamterene and amiloride act at the same part of the tubule by blocking Na$^+$ channels in the cortical collecting tubule.
CLINICAL USE	Hyperaldosteronism, K$^+$ depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen.
ADVERSE EFFECTS	Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects).

The K$^+$ **STA**ys.



Diuretics: electrolyte changes

Urine NaCl	↑ with all diuretics (strength varies based on potency of diuretic effect). Serum NaCl may decrease as a result.
Urine K$^+$	↑ especially with loop and thiazide diuretics. Serum K$^+$ may decrease as a result.
Blood pH	↓ (**acidemia**): carbonic anhydrase inhibitors: ↓ HCO$_3^-$ reabsorption. K$^+$ sparing: aldosterone blockade prevents K$^+$ secretion and H$^+$ secretion. Additionally, hyperkalemia leads to K$^+$ entering all cells (via H$^+$/K$^+$ exchanger) in exchange for H$^+$ exiting cells. ↑ (**alkalemia**): loop diuretics and thiazides cause alkalemia through several mechanisms: ▪ Volume contraction → ↑ AT II → ↑ Na$^+$/H$^+$ exchange in PCT → ↑ HCO$_3^-$ reabsorption (“contraction alkalosis”) ▪ K$^+$ loss leads to K$^+$ exiting all cells (via H$^+$/K$^+$ exchanger) in exchange for H$^+$ entering cells ▪ In low K$^+$ state, H$^+$ (rather than K$^+$) is exchanged for Na$^+$ in cortical collecting tubule → alkalosis and “paradoxical aciduria”
Urine Ca^{2+}	↑ with loop diuretics: ↓ paracellular Ca^{2+} reabsorption → hypocalcemia. ↓ with thiazides: enhanced Ca^{2+} reabsorption.

Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril, ramipril.	
MECHANISM	Inhibit ACE → ↓ AT II → ↓ GFR by preventing constriction of efferent arterioles. ↑ renin due to loss of negative feedback. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator.	
CLINICAL USE	Hypertension, HF (↓ mortality), proteinuria, diabetic nephropathy. Prevent unfavorable heart remodeling as a result of chronic hypertension.	In chronic kidney disease (eg, diabetic nephropathy), ↓ intraglomerular pressure, slowing GBM thickening.
ADVERSE EFFECTS	**C**ough, **A**ngioedema (due to ↑ bradykinin; contraindicated in C1 esterase inhibitor deficiency), **T**eratogen (fetal renal malformations), ↑ **C**reatinine (↓ GFR), **H**yperkalemia, and **H**ypotension. Used with caution in bilateral renal artery stenosis because ACE inhibitors will further ↓ GFR → renal failure.	Captopril's **CATCHH**.

Angiotensin II receptor blockers	Losartan, candesartan, valsartan.
MECHANISM	Selectively block binding of angiotensin II to AT_1 receptor. Effects similar to ACE inhibitors, but ARBs do not increase bradykinin.
CLINICAL USE	Hypertension, HF, proteinuria, or chronic kidney disease (eg, diabetic nephropathy) with intolerance to ACE inhibitors (eg, cough, angioedema).
ADVERSE EFFECTS	Hyperkalemia, ↓ GFR, hypotension; teratogen.

Aliskiren	
MECHANISM	Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I.
CLINICAL USE	Hypertension.
ADVERSE EFFECTS	Hyperkalemia, ↓ GFR, hypotension, angioedema. Relatively contraindicated in patients already taking ACE inhibitors or ARBs.

NOTES

HIGH-YIELD SYSTEMS

Reproductive

"Artificial insemination is when the farmer does it to the cow instead of the bull."

—Student essay

"Whoever called it necking was a poor judge of anatomy."

—Groucho Marx

"See, the problem is that God gives men a brain and a penis, and only enough blood to run one at a time."

—Robin Williams

"I think you can say that life is a system in which proteins and nucleic acids interact in ways that allow the structure to grow and reproduce. It's that growth and reproduction, the ability to make more of yourself, that's important."

—Andrew H. Knoll

▸ Embryology 580

▸ Anatomy 591

▸ Physiology 595

▸ Pathology 603

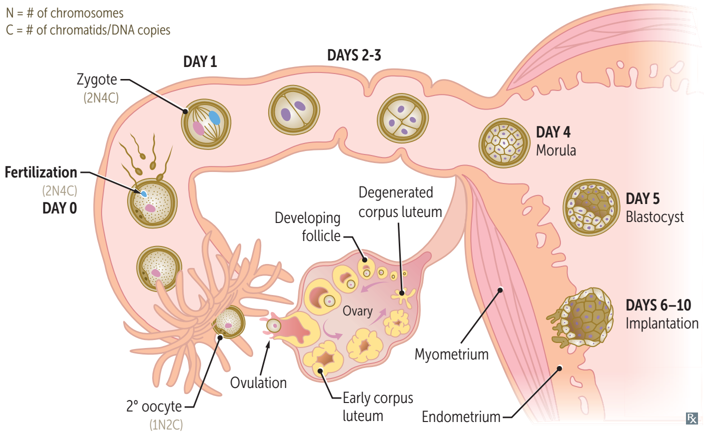
▸ Pharmacology 620

▸ REPRODUCTIVE—EMBRYOLOGY

Important genes of embryogenesis

Sonic hedgehog gene	Produced at base of limbs in zone of polarizing activity. Involved in patterning along anteroposterior axis and CNS development; mutation can cause holoprosencephaly.
***Wnt-7* gene**	Produced at apical ectodermal ridge (thickened ectoderm at distal end of each developing limb). Necessary for proper organization along dorsal-ventral axis.
***FGF* gene**	Produced at apical ectodermal ridge. Stimulates mitosis of underlying mesoderm, providing for lengthening of limbs.
Homeobox (Hox) genes	Involved in segmental organization of embryo in a craniocaudal direction. Code for transcription factors. Hox mutations → appendages in wrong locations.

Early fetal development

Early embryonic development	 N = # of chromosomes C = # of chromatids/DNA copies DAY 1 DAYS 2-3 Zygote (2N4C) DAY 4 Morula Fertilization (2N4C) DAY 0 Degenerated corpus luteum Developing follicle DAY 5 Blastocyst Ovary DAYS 6–10 Implantation Myometrium Ovulation Early corpus luteum 2° oocyte (1N2C) Endometrium	
Within week 1	hCG secretion begins around the time of implantation of blastocyst.	Blastocyst "sticks" at day 6.
Within week 2	Bilaminar disc (epiblast, hypoblast).	2 weeks = 2 layers.
Within week 3	Gastrulation forms trilaminar embryonic disc. Cells from epiblast invaginate → primitive streak → endoderm, mesoderm, ectoderm. Notochord arises from midline mesoderm; overlying ectoderm becomes neural plate.	3 weeks = 3 layers.
Weeks 3–8 (embryonic period)	Neural tube formed by neuroectoderm and closes by week 4. Organogenesis.	Extremely susceptible to teratogens.
Week 4	Heart begins to beat. Upper and lower limb buds begin to form.	4 weeks = 4 limbs and 4 heart chambers.
Week 6	Fetal cardiac activity visible by transvaginal ultrasound.	
Week 8	Fetal movements start.	Gait at week 8.
Week 10	Genitalia have male/female characteristics.	Tenitalia

Embryologic derivatives

Ectoderm		External/outer layer
Surface ectoderm	Epidermis; adenohypophysis (from Rathke pouch); lens of eye; epithelial linings of oral cavity, sensory organs of ear, and olfactory epithelium; anal canal below the pectinate line; parotid, sweat, mammary glands.	**Craniopharyngioma**—benign Rathke pouch tumor with cholesterol crystals, calcifications.
Neural tube	Brain (neurohypophysis, CNS neurons, oligodendrocytes, astrocytes, ependymal cells, pineal gland), retina, spinal cord.	Neuroectoderm—think CNS.
Neural crest	PNS (dorsal root ganglia, cranial nerves, autonomic ganglia, Schwann cells), melanocytes, chromaffin cells of adrenal medulla, parafollicular (C) cells of thyroid, pia and arachnoid, bones of the skull, odontoblasts, aorticopulmonary septum, endocardial cushions, myenteric (Auerbach) plexus.	Neural crest—think PNS and non-neural structures nearby.
Mesoderm	Muscle, bone, connective tissue, serous linings of body cavities (eg, peritoneum), spleen (derived from foregut mesentery), cardiovascular structures, lymphatics, blood, wall of gut tube, upper vagina, kidneys, adrenal cortex, dermis, testes, ovaries. Notochord induces ectoderm to form neuroectoderm (neural plate). Its only postnatal derivative is the nucleus pulposus of the intervertebral disc.	Middle/"meat" layer. Mesodermal defects = **VACTERL**: Vertebral defects Anal atresia Cardiac defects Tracheo-Esophageal fistula Renal defects Limb defects (bone and muscle)
Endoderm	Gut tube epithelium (including anal canal above the pectinate line), most of urethra and lower vagina (derived from urogenital sinus), luminal epithelial derivatives (eg, lungs, liver, gallbladder, pancreas, eustachian tube, thymus, parathyroid, thyroid follicular cells).	"Enternal" layer.

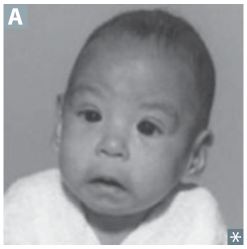
Types of errors in morphogenesis

Agenesis	Absent organ due to absent primordial tissue.
Aplasia	Absent organ despite presence of primordial tissue.
Hypoplasia	Incomplete organ development; primordial tissue present.
Disruption	2° breakdown of previously normal tissue or structure (eg, amniotic band syndrome).
Deformation	Extrinsic disruption; occurs after embryonic period.
Malformation	Intrinsic disruption; occurs during embryonic period (weeks 3–8).
Sequence	Abnormalities result from a single 1° embryologic event (eg, oligohydramnios → Potter sequence).

Teratogens Most susceptible in 3rd–8th weeks (embryonic period—organogenesis) of pregnancy. Before week 3, "all-or-none" effects. After week 8, growth and function affected.

TERATOGEN	EFFECTS ON FETUS	NOTES
Medications		
ACE inhibitors	Renal damage	
Alkylating agents	Absence of digits, multiple anomalies	
Aminoglycosides	**Oto**toxicity	**A mean guy** hit the baby in the **ear**.
Antiepileptic drugs	Neural tube defects, cardiac defects, cleft palate, skeletal abnormalities (eg, phalanx/nail hypoplasia, facial dysmorphism)	High-dose folate supplementation recommended. Most commonly valproate, carbamazepine, phenytoin, phenobarbital.
Diethylstilbestrol	Vaginal clear cell adenocarcinoma, congenital Müllerian anomalies	
Folate antagonists	Neural tube defects	Includes trimethoprim, methotrexate, antiepileptic drugs.
Isotretinoin	Multiple severe birth defects	Contraception mandatory. Iso**TERAT**inoin.
Lithium	Ebstein anomaly (apical displacement of tricuspid valve)	
Methimazole	Aplasia cutis congenita	
Tetracyclines	Discolored teeth, inhibited bone growth	"**Teeth**racyclines."
Thalidomide	Limb defects (phocomelia, micromelia—"flipper" limbs)	**Limb** defects with "tha-**limb**-domide."
Warfarin	Bone deformities, fetal hemorrhage, abortion, ophthalmologic abnormalities	Do not wage **warfare** on the baby; keep it **hep**py with **hep**arin (does not cross placenta).
Substance abuse		
Alcohol	Common cause of birth defects and intellectual disability; fetal alcohol syndrome	
Cocaine	Low birth weight, preterm birth, IUGR, placental abruption	Cocaine → vasoconstriction.
Smoking (nicotine, CO)	Low birth weight (leading cause in developed countries), preterm labor, placental problems, IUGR, SIDS	Nicotine → vasoconstriction. CO → impaired O_2 delivery.
Other		
Iodine (lack or excess)	Congenital goiter or hypothyroidism (cretinism)	
Maternal diabetes	Caudal regression syndrome (anal atresia to sirenomelia), congenital heart defects, neural tube defects, macrosomia, neonatal hypoglycemia	
Methylmercury	Neurotoxicity	Highest in swordfish, shark, tilefish, king mackerel.
Vitamin A excess	Extremely high risk for spontaneous abortions and birth defects (cleft palate, cardiac)	
X-rays	Microcephaly, intellectual disability	Minimized by lead shielding.

Fetal alcohol syndrome

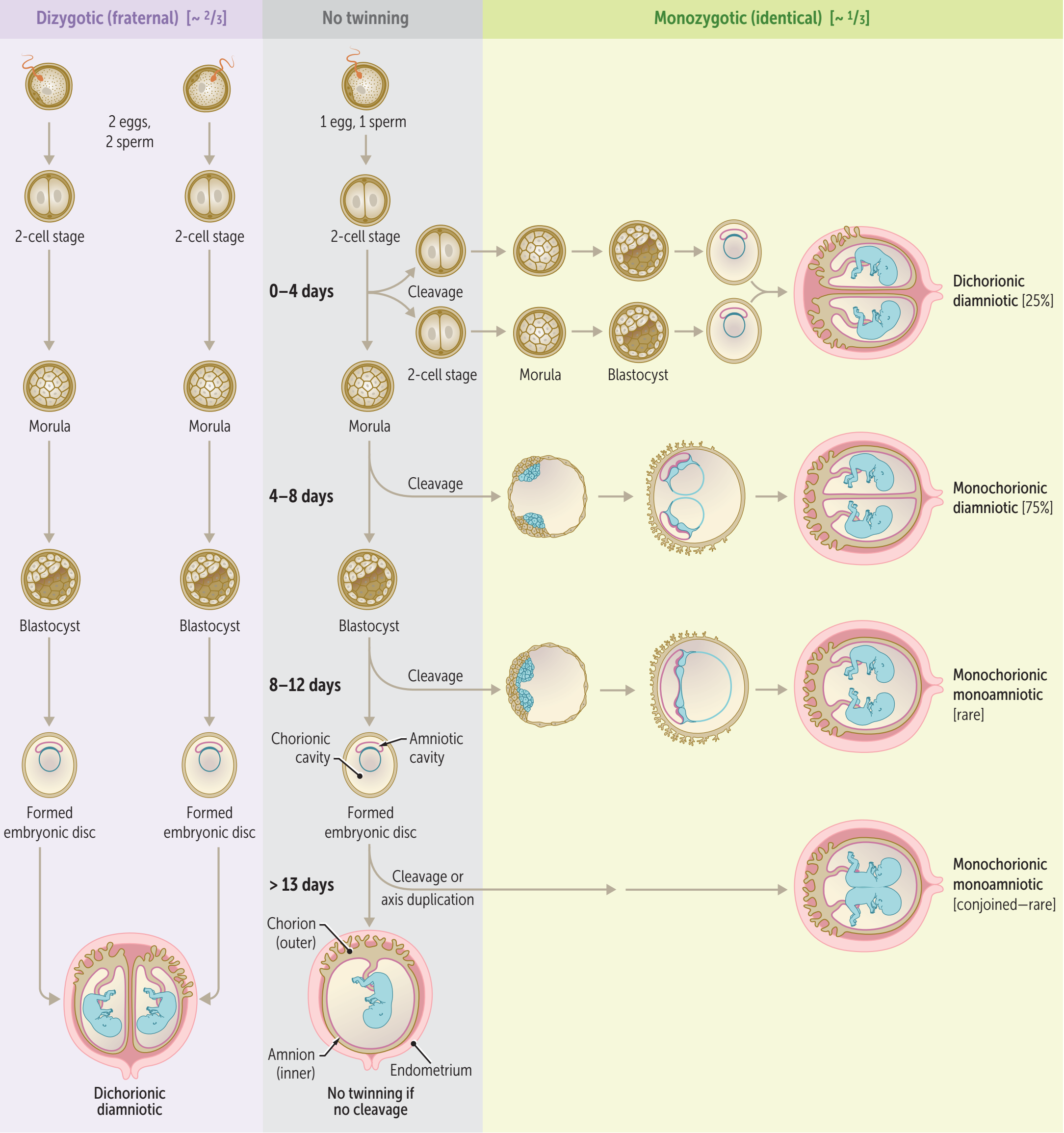


Leading cause of intellectual disability in the US. Newborns of alcohol-consuming mothers have ↑ incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities A (eg, smooth philtrum, thin vermillion border [upper lip], small palpebral fissures), limb dislocation, heart defects. Heart-lung fistulas and holoprosencephaly in most severe form. Mechanism is failure of cell migration.

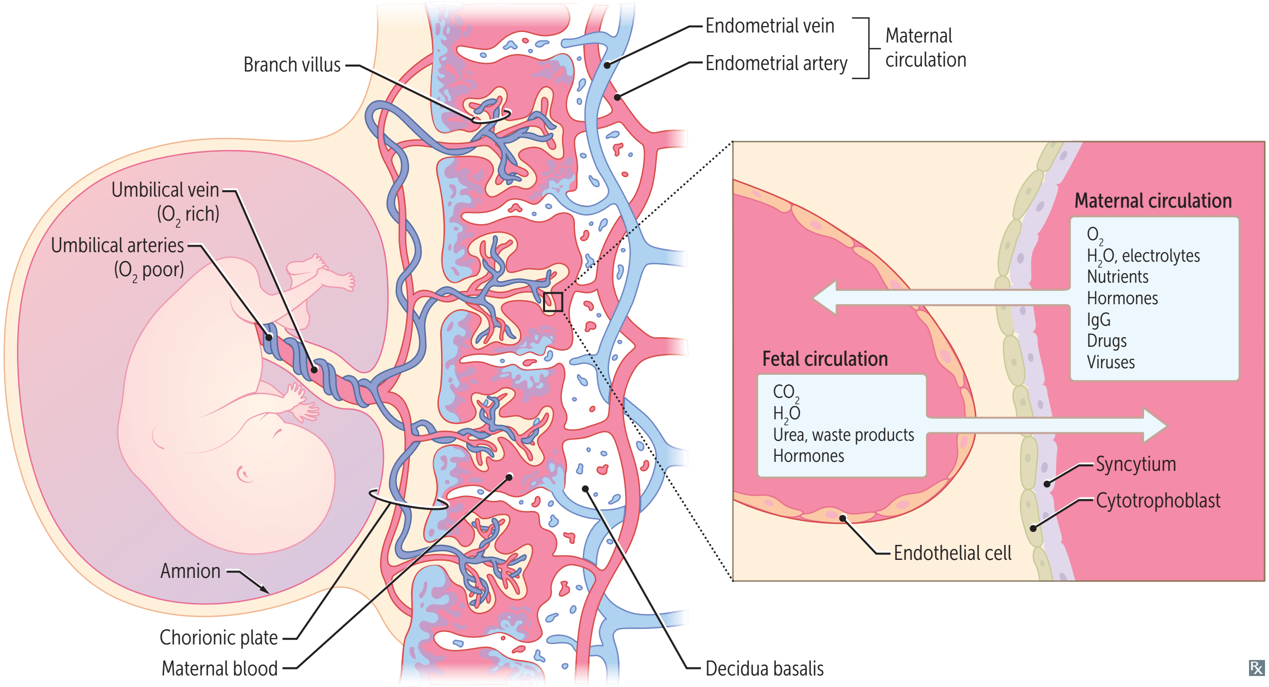
Twinning

Dizygotic ("fraternal") twins arise from 2 eggs that are separately fertilized by 2 different sperm (always 2 zygotes) and will have 2 separate amniotic sacs and 2 separate placentas (chorions).

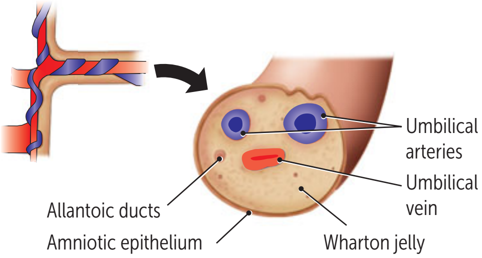
Monozygotic ("identical") twins arise from 1 fertilized egg (1 egg + 1 sperm) that splits in early pregnancy. The timing of cleavage determines chorionicity (number of chorions) and amnionicity (number of amnions).

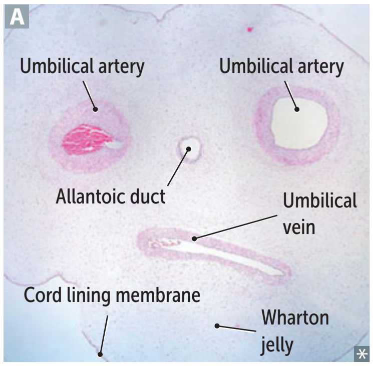

Dizygotic (fraternal) [~ 2/3]
No twinning
Monozygotic (identical) [~ 1/3]
2 eggs, 2 sperm
1 egg, 1 sperm
2-cell stage
2-cell stage
2-cell stage
0–4 days
Cleavage
2-cell stage
Morula
Blastocyst
Dichorionic diamniotic [25%]
Morula
Morula
Morula
4–8 days
Cleavage
Monochorionic diamniotic [75%]
Blastocyst
Blastocyst
Blastocyst
8–12 days
Cleavage
Monochorionic monoamniotic [rare]
Chorionic cavity
Amniotic cavity
Formed embryonic disc
Formed embryonic disc
Formed embryonic disc
> 13 days
Cleavage or axis duplication
Monochorionic monoamniotic [conjoined—rare]
Chorion (outer)
Amnion (inner)
Endometrium
Dichorionic diamniotic
No twinning if no cleavage

Placenta	1° site of nutrient and gas exchange between mother and fetus.	
Fetal component		
Cytotrophoblast	Inner layer of chorionic villi.	**C**ytotrophoblast makes **C**ells.
Syncytiotrophoblast	Outer layer of chorionic villi; synthesizes and secretes hormones, eg, hCG (structurally similar to LH; stimulates corpus luteum to secrete progesterone during first trimester).	**Syn**cytiotrophoblast **syn**thesizes hormones. Lacks MHC-I expression → ↓ chance of attack by maternal immune system.
Maternal component		
Decidua basalis	Derived from endometrium. Maternal blood in lacunae.	

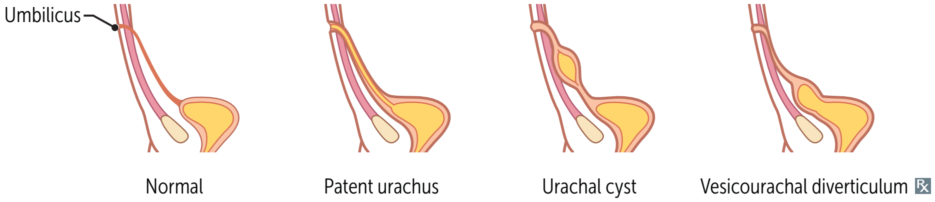

Branch villus
Endometrial vein
Endometrial artery
Maternal circulation
Umbilical vein (O_2 rich)
Umbilical arteries (O_2 poor)
Amnion
Chorionic plate
Maternal blood
Decidua basalis
Maternal circulation
O_2
H_2O, electrolytes
Nutrients
Hormones
IgG
Drugs
Viruses
Fetal circulation
CO_2
H_2O
Urea, waste products
Hormones
Syncytium
Cytotrophoblast
Endothelial cell

Umbilical cord	Umbilical arteries (2)—return deoxygenated blood from fetal internal iliac arteries to placenta A. Umbilical vein (1)—supplies oxygenated blood from placenta to fetus; drains into IVC via liver or via ductus venosus.	Single umbilical artery (2-vessel cord) is associated with congenital and chromosomal anomalies. Umbilical arteries and vein are derived from allantois.


Umbilical arteries
Umbilical vein
Allantoic ducts
Amniotic epithelium
Wharton jelly

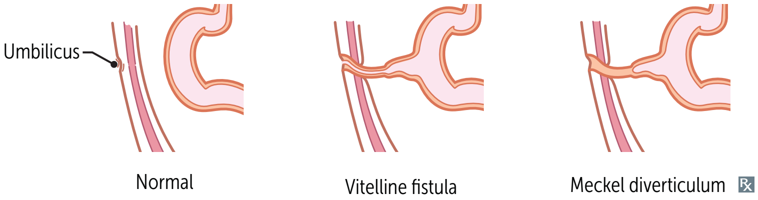

A
Umbilical artery
Umbilical artery
Allantoic duct
Umbilical vein
Cord lining membrane
Wharton jelly

Urachus	In the 3rd week the yolk sac forms the allantois, which extends into urogenital sinus. Allantois becomes the urachus, a duct between fetal bladder and umbilicus.
Patent urachus	Total failure of urachus to obliterate → **u**rine discharge from **u**mbilicus.
Urachal cyst	Partial failure of urachus to obliterate; fluid-filled cavity lined with uroepithelium, between umbilicus and bladder. Can lead to infection, adenocarcinoma.
Vesicourachal diverticulum	Slight failure of urachus to obliterate → outpouching of bladder.



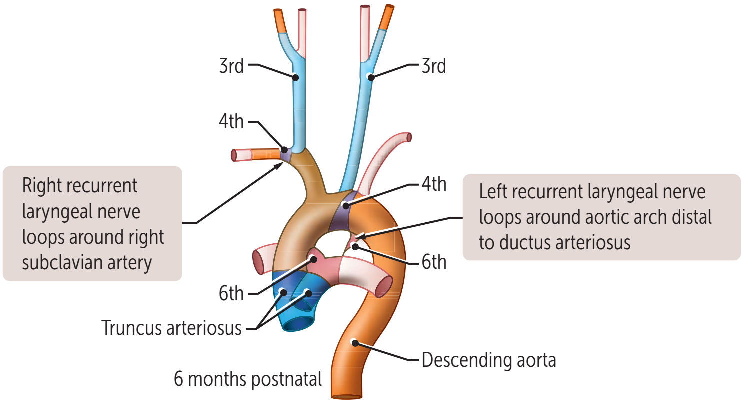
Normal Patent urachus Urachal cyst Vesicourachal diverticulum

Vitelline duct	7th week—obliteration of vitelline duct (omphalomesenteric duct), which connects yolk sac to midgut lumen.
Vitelline fistula	Vitelline duct fails to close → meconium discharge from umbilicus.
Meckel diverticulum	Partial closure of vitelline duct, with patent portion attached to ileum (true diverticulum). May have heterotopic gastric and/or pancreatic tissue → melena, hematochezia, abdominal pain.



Normal Vitelline fistula Meckel diverticulum

Aortic arch derivatives	Develop into arterial system.	
1st	Part of maxillary artery (branch of external carotid).	1st arch is maximal.
2nd	Stapedial artery and hyoid artery.	Second = Stapedial.
3rd	Common Carotid artery and proximal part of internal Carotid artery.	C is 3rd letter of alphabet.
4th	On left, aortic arch; on right, proximal part of right subclavian artery.	4th arch (4 limbs) = systemic.
6th	Proximal part of pulmonary arteries and (on left only) ductus arteriosus.	6th arch = pulmonary and the pulmonary-to-systemic shunt (ductus arteriosus).



Right recurrent laryngeal nerve loops around right subclavian artery

Left recurrent laryngeal nerve loops around aortic arch distal to ductus arteriosus

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Branchial (pharyngeal) apparatus

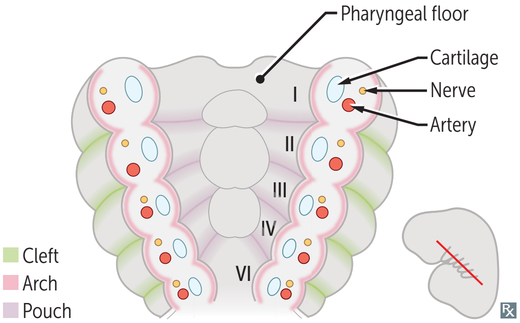
Composed of branchial clefts, arches, pouches.

Branchial clefts—derived from ectoderm. Also called branchial grooves.

Branchial arches—derived from mesoderm (muscles, arteries) and neural crest (bones, cartilage).

Branchial pouches—derived from endoderm.

CAP covers outside to inside:
Clefts = ectoderm
Arches = mesoderm + neural crest
Pouches = endoderm



Branchial cleft derivatives

1st cleft develops into external auditory meatus.

2nd through 4th clefts form temporary cervical sinuses, which are obliterated by proliferation of 2nd arch mesenchyme.

Persistent cervical sinus → branchial cleft cyst within lateral neck, anterior to sternocleidomastoid muscle. Immobile during swallowing.

Branchial arch derivatives

ARCH	CARTILAGE	MUSCLES	NERVES[a]	ABNORMALITIES/COMMENTS
1st arch	Maxillary process → Maxilla, zygoMatic bone Mandibular process → Meckel cartilage → Mandible, Malleus and incus, sphenoMandibular ligament	Muscles of Mastication (temporalis, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, anterior ⅔ of tongue	CN V_2 and V_3 chew	Pierre Robin sequence—micrognathia, glossoptosis, cleft palate, airway obstruction Treacher Collins syndrome—neural crest dysfunction → mandibular hypoplasia, facial abnormalities
2nd arch	Reichert cartilage: Stapes, Styloid process, lesser horn of hyoid, Stylohyoid ligament	Muscles of facial expression, Stapedius, Stylohyoid, platySma, posterior belly of digastric	CN VII (facial expression) smile	
3rd arch	Greater horn of hyoid	Stylopharyngeus (think of stylopharyngeus innervated by glossopharyngeal nerve)	CN IX (stylo-pharyngeus) swallow stylishly	
4th–6th arches	Arytenoids, Cricoid, Corniculate, Cuneiform, Thyroid (used to sing and ACCCT)	4th arch: most pharyngeal constrictors; cricothyroid, levator veli palatini 6th arch: all intrinsic muscles of larynx except cricothyroid	4th arch: CN X (superior laryngeal branch) simply swallow 6th arch: CN X (recurrent laryngeal branch) speak	Arches 3 and 4 form posterior ⅓ of tongue; arch 5 makes no major developmental contributions

[a] These are the only CNs with both motor and sensory components (except V_2, which is sensory only).

When at the restaurant of the golden arches, children tend to first chew (1), then smile (2), then swallow stylishly (3) or simply swallow (4), and then speak (6).

Branchial pouch derivatives

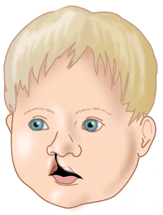
POUCH	DERIVATIVES	NOTES	MNEMONIC
1st pouch	Middle ear cavity, eustachian tube, mastoid air cells.	1st pouch contributes to endoderm-lined structures of ear.	**Ear**, **tonsils**, **bottom-to-top**: 1 (**ear**), 2 (**tonsils**), 3 dorsal (**bottom** for inferior parathyroids), 3 ventral (**t**o = **t**hymus), 4 (**top** = superior parathyroids).
2nd pouch	Epithelial lining of palatine tonsil.		
3rd pouch	Dorsal wings → **inferior** parathyroids. Ventral wings → thymus.	**3**rd pouch contributes to **3** structures (thymus, left and right inferior parathyroids). 3rd-pouch structures end up **below** 4th-pouch structures.	
4th pouch	Dorsal wings → **superior** parathyroids. Ventral wings → ultimobranchial body → parafollicular (C) cells of thyroid.		
DiGeorge syndrome	Chromosome 22q11 deletion. Aberrant development of 3rd and 4th pouches → T-cell deficiency (thymic aplasia) and hypocalcemia (failure of parathyroid development). Associated with cardiac defects (conotruncal anomalies).		

Cleft lip and cleft palate

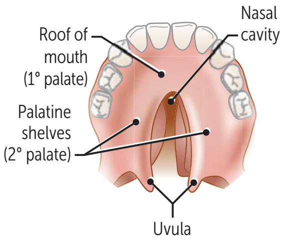
Cleft lip—failure of fusion of the maxillary and medial nasal processes (formation of 1° palate).

Cleft palate—failure of fusion of the two lateral palatine shelves or failure of fusion of lateral palatine shelves with the nasal septum and/or median palatine shelf (formation of 2° palate).

Cleft lip and cleft palate have distinct, multifactorial etiologies, but often occur together.



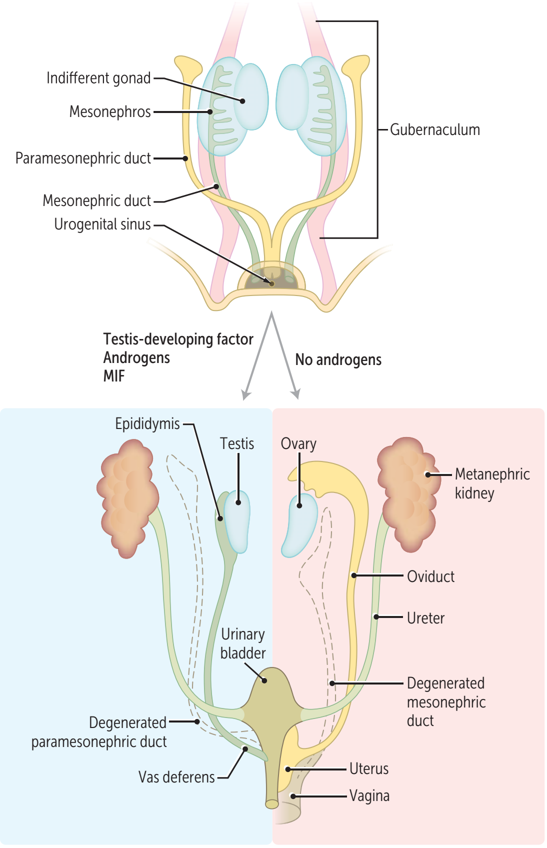
Cleft lip



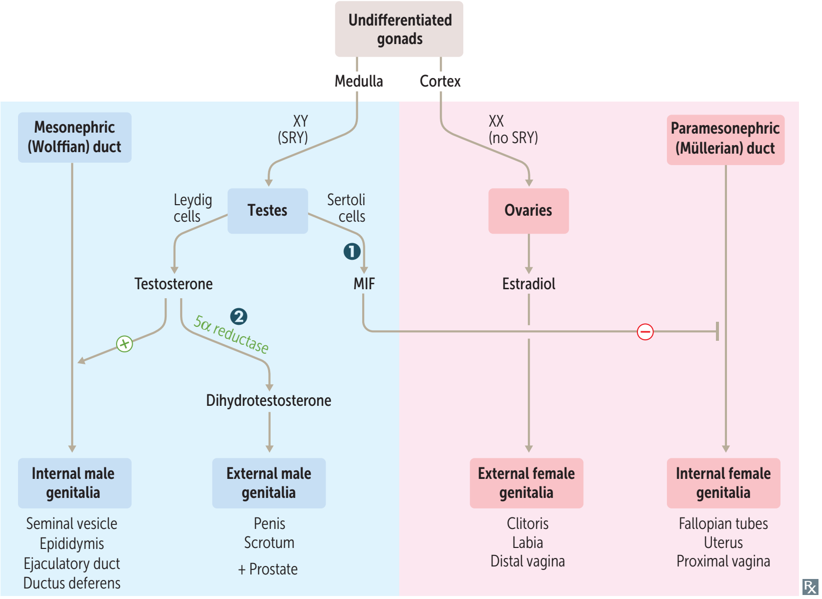
Cleft palate (partial)

Genital embryology

Female	Default development. Mesonephric duct degenerates and paramesonephric duct develops.
Male	*SRY* gene on Y chromosome—produces testis-determining factor → testes development. Sertoli cells secrete Müllerian inhibitory factor (MIF) that suppresses development of paramesonephric ducts. Leydig cells secrete androgens that stimulate development of mesonephric ducts.
Paramesonephric (Müllerian) duct	Develops into female internal structures—fallopian tubes, uterus, upper portion of vagina (lower portion from urogenital sinus). Male remnant is appendix testis. Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome)—may present as 1° amenorrhea (due to a lack of uterine development) in females with fully developed 2° sexual characteristics (functional ovaries).
Mesonephric (Wolffian) duct	Develops into male internal structures (except prostate)—**S**eminal vesicles, **E**pididymis, **E**jaculatory duct, **D**uctus deferens (**SEED**). In females, remnant of mesonephric duct → Gartner duct.


Indifferent gonad
Mesonephros
Paramesonephric duct
Mesonephric duct
Urogenital sinus
Gubernaculum
Testis-developing factor
Androgens
MIF
No androgens
Epididymis
Testis
Ovary
Metanephric kidney
Oviduct
Ureter
Urinary bladder
Degenerated mesonephric duct
Degenerated paramesonephric duct
Vas deferens
Uterus
Vagina

Sexual determination


Undifferentiated gonads
Medulla
Cortex
XY (SRY)
XX (no SRY)
Mesonephric (Wolffian) duct
Paramesonephric (Müllerian) duct
Leydig cells
Testes
Sertoli cells
Ovaries
❶
Testosterone
MIF
Estradiol
⊕
❷
5α reductase
⊖
Dihydrotestosterone
Internal male genitalia
Seminal vesicle
Epididymis
Ejaculatory duct
Ductus deferens
External male genitalia
Penis
Scrotum
+ Prostate
External female genitalia
Clitoris
Labia
Distal vagina
Internal female genitalia
Fallopian tubes
Uterus
Proximal vagina

❶ No Sertoli cells or lack of Müllerian inhibitory factor → develop both male and female internal genitalia and male external genitalia

❷ 5α-reductase deficiency—inability to convert testosterone into DHT → male internal genitalia, ambiguous external genitalia until puberty (when ↑ testosterone levels cause masculinization)

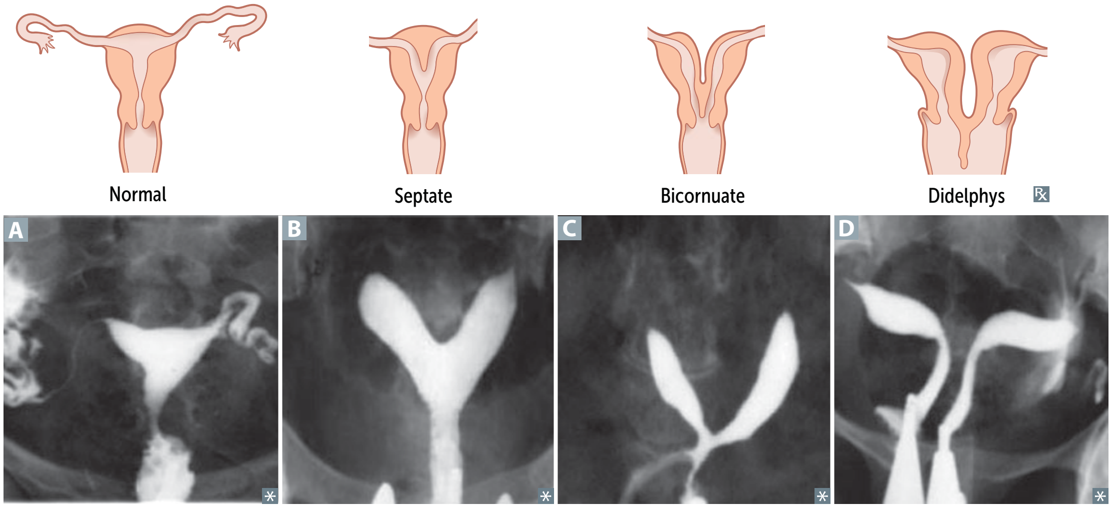
In the testes:

Leydig **L**eads to male (internal and external) sexual differentiation.

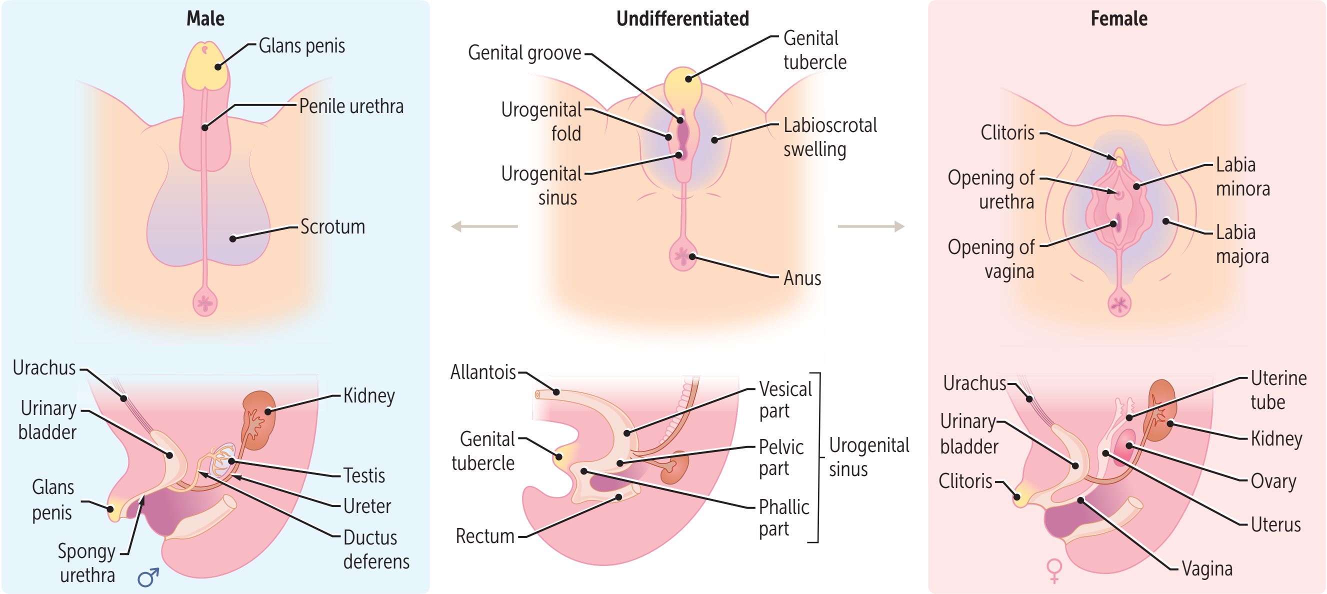
Sertoli **S**huts down female (internal) sexual differentiation.

Uterine (Müllerian duct) anomalies

Septate uterus	Common anomaly vs normal uterus A. Incomplete resorption of septum B. ↓ fertility and early miscarriage/pregnancy loss. Treat with septoplasty.
Bicornuate uterus	Incomplete fusion of Müllerian ducts C. ↑ risk of complicated pregnancy, early pregnancy loss, malpresentation, prematurity.
Uterus didelphys	Complete failure of fusion → double uterus, cervix, vagina D. Pregnancy possible.


Normal
Septate
Bicornuate
Didelphys
℞
A
B
C
D

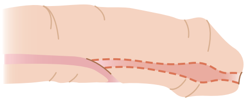
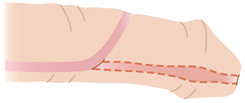
Male/female genital homologs


Male
Glans penis
Penile urethra
Scrotum
Urachus
Urinary bladder
Kidney
Glans penis
Testis
Ureter
Spongy urethra
Ductus deferens
♂
Undifferentiated
Genital groove
Genital tubercle
Urogenital fold
Labioscrotal swelling
Urogenital sinus
Anus
Allantois
Vesical part
Genital tubercle
Pelvic part
Urogenital sinus
Phallic part
Rectum
Female
Clitoris
Labia minora
Opening of urethra
Labia majora
Opening of vagina
Urachus
Uterine tube
Urinary bladder
Kidney
Clitoris
Ovary
Uterus
Vagina
♀

	Dihydrotestosterone		Estrogen	
Glans penis	←	Genital tubercle	→	Glans clitoris
Corpus cavernosum and spongiosum	←	Genital tubercle	→	Vestibular bulbs
Bulbourethral glands (of Cowper)	←	Urogenital sinus	→	Greater vestibular glands (of Bartholin)
Prostate gland	←	Urogenital sinus	→	Urethral and paraurethral glands (of Skene)
Ventral shaft of penis (penile urethra)	←	Urogenital folds	→	Labia minora
Scrotum	←	Labioscrotal swelling	→	Labia majora

℞

Congenital penile abnormalities

Hypospadias 	Abnormal opening of penile urethra on ventral surface of penis due to failure of urethral folds to fuse.	Hypospadias is more common than epispadias. Associated with inguinal hernia and cryptorchidism. **Hypo** is **below**.
Epispadias 	Abnormal opening of penile urethra on dorsal surface of penis due to faulty positioning of genital tubercle.	**E**xstrophy of the bladder is associated with **E**pispadias. When you have **E**pispadias, you hit your **E**ye when you p**EE**.

Descent of testes and ovaries

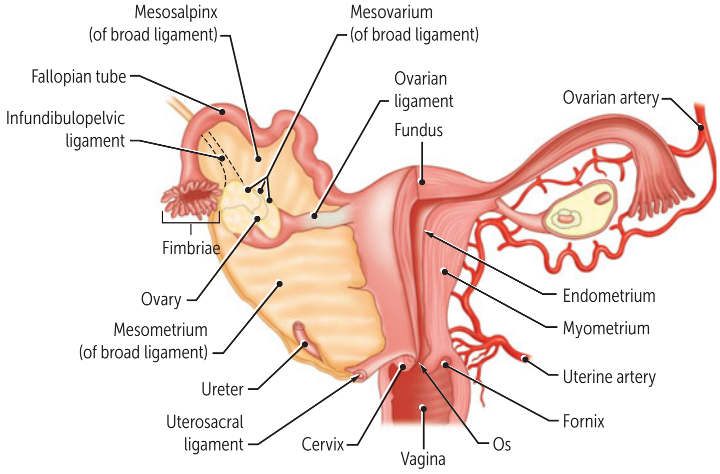
	MALE REMNANT	FEMALE REMNANT
Gubernaculum (band of fibrous tissue)	Anchors testes within scrotum.	Ovarian ligament + round ligament of uterus.
Processus vaginalis (evagination of peritoneum)	Forms tunica vaginalis.	Obliterated.

▸ REPRODUCTIVE—ANATOMY

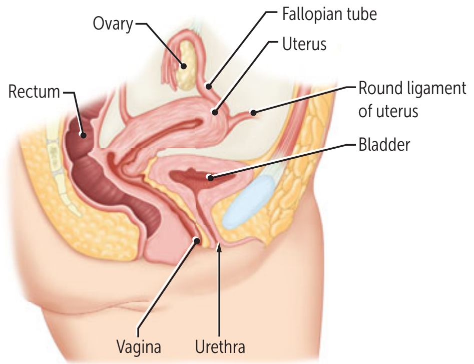
Gonadal drainage

Venous drainage	Left ovary/testis → left gonadal vein → left renal vein → IVC. Right ovary/testis → right gonadal vein → IVC.	"**L**eft gonadal vein takes the **L**ongest way." Because the left spermatic vein enters the left renal vein at a 90° angle, flow is less laminar on left than on right → left venous pressure > right venous pressure → varicocele more common on the left.
Lymphatic drainage	Ovaries/testes → para-aortic lymph nodes. Body of uterus/cervix/superior bladder → external iliac nodes. Prostate/cervix/corpus cavernosum/proximal vagina → internal iliac nodes. Distal vagina/vulva/scrotum/distal anus → superficial inguinal nodes. Glans penis → deep inguinal nodes.	

Female reproductive anatomy


Mesosalpinx (of broad ligament)
Mesovarium (of broad ligament)
Fallopian tube
Infundibulopelvic ligament
Ovarian ligament
Fundus
Ovarian artery
Fimbriae
Ovary
Mesometrium (of broad ligament)
Ureter
Uterosacral ligament
Cervix
Vagina
Os
Endometrium
Myometrium
Uterine artery
Fornix

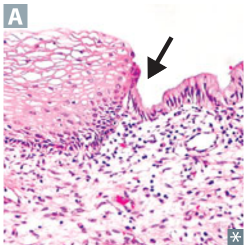
Posterior view


Ovary
Fallopian tube
Uterus
Rectum
Round ligament of uterus
Bladder
Vagina
Urethra

Sagittal view

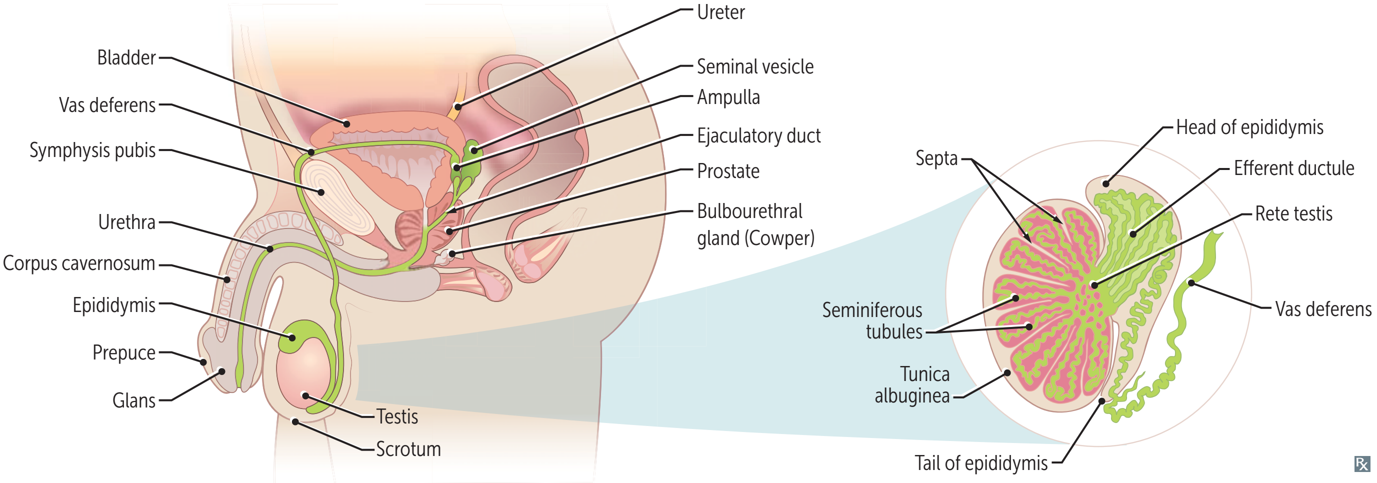
LIGAMENT	CONNECTS	STRUCTURES CONTAINED	NOTES
Infundibulopelvic ligament (suspensory ligament of the ovary)	Ovaries to lateral pelvic wall	Ovarian vessels	Ligate vessels during oophorectomy to avoid bleeding. Ureter courses retroperitoneally, close to gonadal vessels → at risk of injury during ligation of ovarian vessels.
Cardinal ligament (not labeled)	Cervix to side wall of pelvis	Uterine vessels	Ureter at risk of injury during ligation of uterine vessels in hysterectomy.
Round ligament of the uterus	Uterine fundus to labia majora		Derivative of gubernaculum. Travels through round inguinal canal; above the artery of Sampson.
Broad ligament	Uterus, fallopian tubes, and ovaries to pelvic side wall	Ovaries, fallopian tubes, round ligaments of uterus	Fold of peritoneum that comprises the mesosalpinx, mesometrium, and mesovarium.
Ovarian ligament	Medial pole of ovary to lateral uterus	—	Derivative of gubernaculum. Ovarian Ligament Latches to Lateral uterus.

Female reproductive epithelial histology



TISSUE	HISTOLOGY/NOTES
Vagina	Stratified squamous epithelium, nonkeratinized
Ectocervix	Stratified squamous epithelium, nonkeratinized
Transformation zone	Squamocolumnar junction A (most common area for cervical cancer)
Endocervix	Simple columnar epithelium
Uterus	Simple columnar epithelium with long tubular glands in proliferative phase; coiled glands in secretory phase
Fallopian tube	Simple columnar epithelium, ciliated
Ovary, outer surface	Simple cuboidal epithelium (germinal epithelium covering surface of ovary)

Male reproductive anatomy


Bladder
Vas deferens
Symphysis pubis
Urethra
Corpus cavernosum
Epididymis
Prepuce
Glans
Testis
Scrotum
Ureter
Seminal vesicle
Ampulla
Ejaculatory duct
Prostate
Bulbourethral gland (Cowper)
Septa
Head of epididymis
Efferent ductule
Rete testis
Vas deferens
Seminiferous tubules
Tunica albuginea
Tail of epididymis

Pathway of sperm during ejaculation—**SEVEN UP**:

Seminiferous tubules
Epididymis
Vas deferens
Ejaculatory ducts
(**N**othing)
Urethra
Penis

Urethral injury

Suspect if blood seen at urethral meatus. Urethral catheterization relatively contraindicated.

Posterior urethra—membranous urethra prone to injury from pelvic fracture. Injury can cause urine to leak into retropubic space.

Anterior urethra—bulbar urethra at risk of damage due to perineal straddle injury. Can cause urine to leak beneath deep fascia of Buck. If fascia is torn, urine escapes into superficial perineal space.

Autonomic innervation of the male sexual response

Erection—**P**arasympathetic nervous system (pelvic nerve):

- NO → ↑ cGMP → smooth muscle relaxation → vasodilation → proerectile.
- Norepinephrine → ↑ $[\text{Ca}^{2+}]_{\text{in}}$ → smooth muscle contraction → vasoconstriction → antierectile.

Emission—**S**ympathetic nervous system (hypogastric nerve).

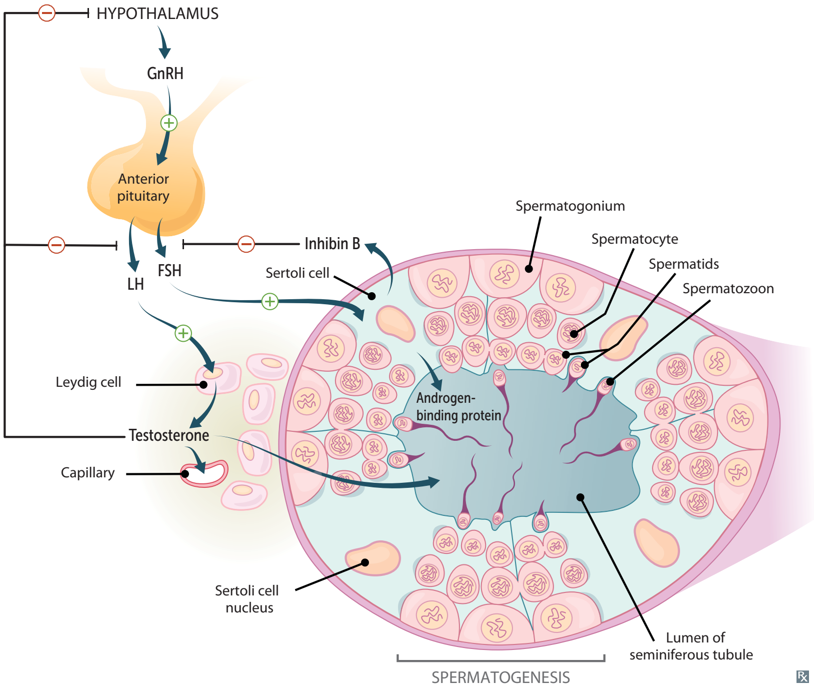
Ejaculation—visceral and **S**omatic nerves (pudendal nerve).

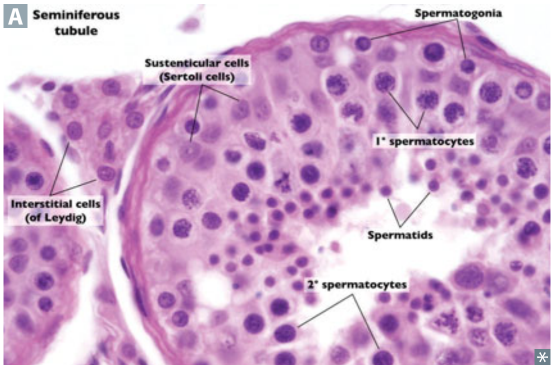
Point, **S**queeze, and **S**hoot.

PDE-5 inhibitors (eg, sildenafil) ↓ cGMP breakdown.

Seminiferous tubules

CELL	FUNCTION	LOCATION/NOTES
Spermatogonia (germ cells)	Maintain germ cell pool and produce 1° spermatocytes.	Line seminiferous tubules A
Sertoli cells (non–germ cells)	Secrete inhibin B → inhibit FSH. Secrete androgen-binding protein → maintain local levels of testosterone. Produce MIF. Tight junctions between adjacent Sertoli cells form blood-testis barrier → isolate gametes from autoimmune attack. Support and nourish developing spermatozoa. Regulate spermatogenesis. Temperature sensitive; ↓ sperm production and ↓ inhibin B with ↑ temperature.	Line seminiferous tubules Convert testosterone and androstenedione to estrogens via aromatase **S**ertoli cells **S**upport **S**perm **S**ynthesis Homolog of female granulosa cells ↑ temperature seen in varicocele, cryptorchidism
Leydig cells (endocrine cells)	Secrete testosterone in the presence of LH; testosterone production unaffected by temperature.	Interstitium Homolog of female theca interna cells

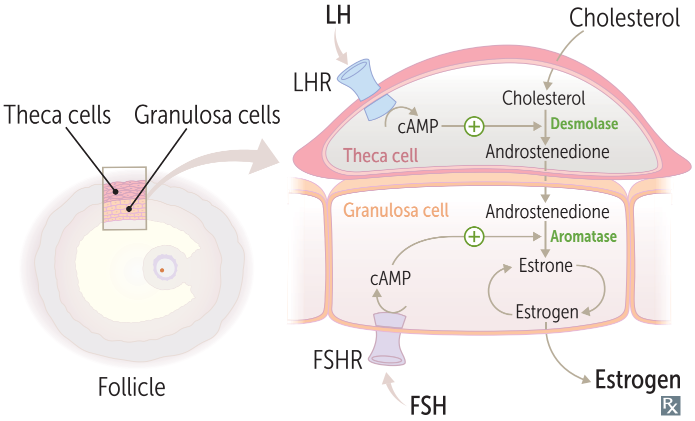

HYPOTHALAMUS
GnRH
Anterior pituitary
LH
FSH
Inhibin B
Sertoli cell
Leydig cell
Testosterone
Capillary
Sertoli cell nucleus
Spermatogonium
Spermatocyte
Spermatids
Spermatozoon
Androgen-binding protein
Lumen of seminiferous tubule
SPERMATOGENESIS


A Seminiferous tubule
Spermatogonia
Sustenticular cells (Sertoli cells)
1° spermatocytes
Interstitial cells (of Leydig)
Spermatids
2° spermatocytes

▶ REPRODUCTIVE—PHYSIOLOGY

Estrogen

SOURCE	Ovary (17β-estradiol), placenta (estriol), adipose tissue (estrone via aromatization).	Potency: estradiol > estrone > estriol
FUNCTION	Development of genitalia and breast, female fat distribution. Growth of follicle, endometrial proliferation, ↑ myometrial excitability. Upregulation of estrogen, LH, and progesterone receptors; feedback inhibition of FSH and LH, then LH surge; stimulation of prolactin secretion. ↑ transport proteins, SHBG; ↑ HDL; ↓ LDL.	Pregnancy: ▪ 50-fold ↑ in estradiol and estrone ▪ 1000-fold ↑ in estriol (indicator of fetal well-being) Estrogen receptors expressed in cytoplasm; translocate to nucleus when bound by estrogen


LH
Cholesterol
LHR
Cholesterol
Desmolase
cAMP
Theca cell
Androstenedione
Theca cells
Granulosa cells
Granulosa cell
Androstenedione
Aromatase
Estrone
cAMP
Estrogen
FSHR
Follicle
FSH
Estrogen
Rx

Progesterone

SOURCE	Corpus luteum, placenta, adrenal cortex, testes.	Fall in progesterone after delivery disinhibits prolactin → lactation. ↑ progesterone is indicative of ovulation. **Progest**erone is **pro-gest**ation. **Prolact**in is **pro-lact**ation.
FUNCTION	Stimulation of endometrial glandular secretions and spiral artery development. Maintenance of pregnancy. ↓ myometrial excitability. Production of thick cervical mucus, which inhibits sperm entry into uterus. ↑ body temperature. Inhibition of gonadotropins (LH, FSH). Uterine smooth muscle relaxation (preventing contractions). ↓ estrogen receptor expression. Prevents endometrial hyperplasia.	

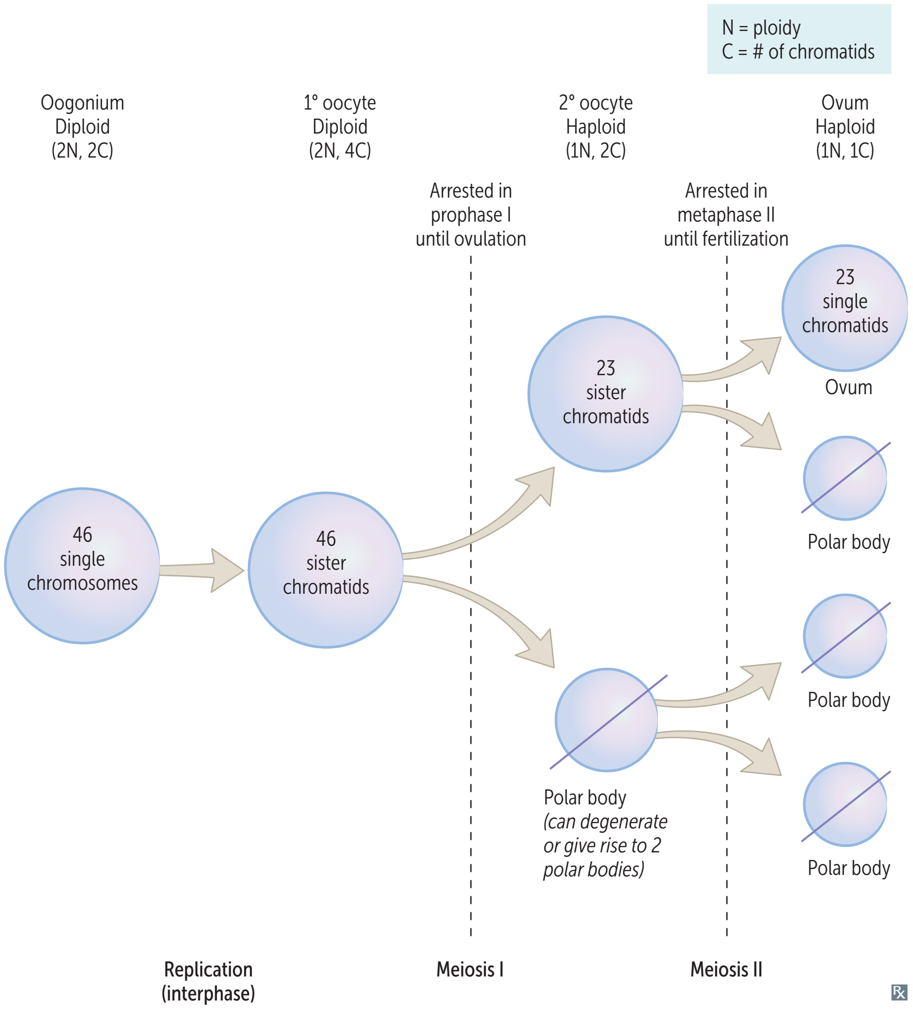
Oogenesis

1° oocytes begin meiosis I during fetal life and complete meiosis I just prior to ovulation.

Meiosis I is arrested in pr**O**phase I for years until **O**vulation (1° oocytes).

Meiosis II is arrested in **met**aphase II until fertilization (2° oocytes). “An egg **met** a sperm.”

If fertilization does not occur within 1 day, the 2° oocyte degenerates.


N = ploidy
C = # of chromatids
Oogonium
Diploid
(2N, 2C)
1° oocyte
Diploid
(2N, 4C)
2° oocyte
Haploid
(1N, 2C)
Ovum
Haploid
(1N, 1C)
Arrested in prophase I until ovulation
Arrested in metaphase II until fertilization
46 single chromosomes
46 sister chromatids
23 sister chromatids
23 single chromatids
Ovum
Polar body
Polar body
Polar body
Polar body
(can degenerate or give rise to 2 polar bodies)
Replication (interphase)
Meiosis I
Meiosis II

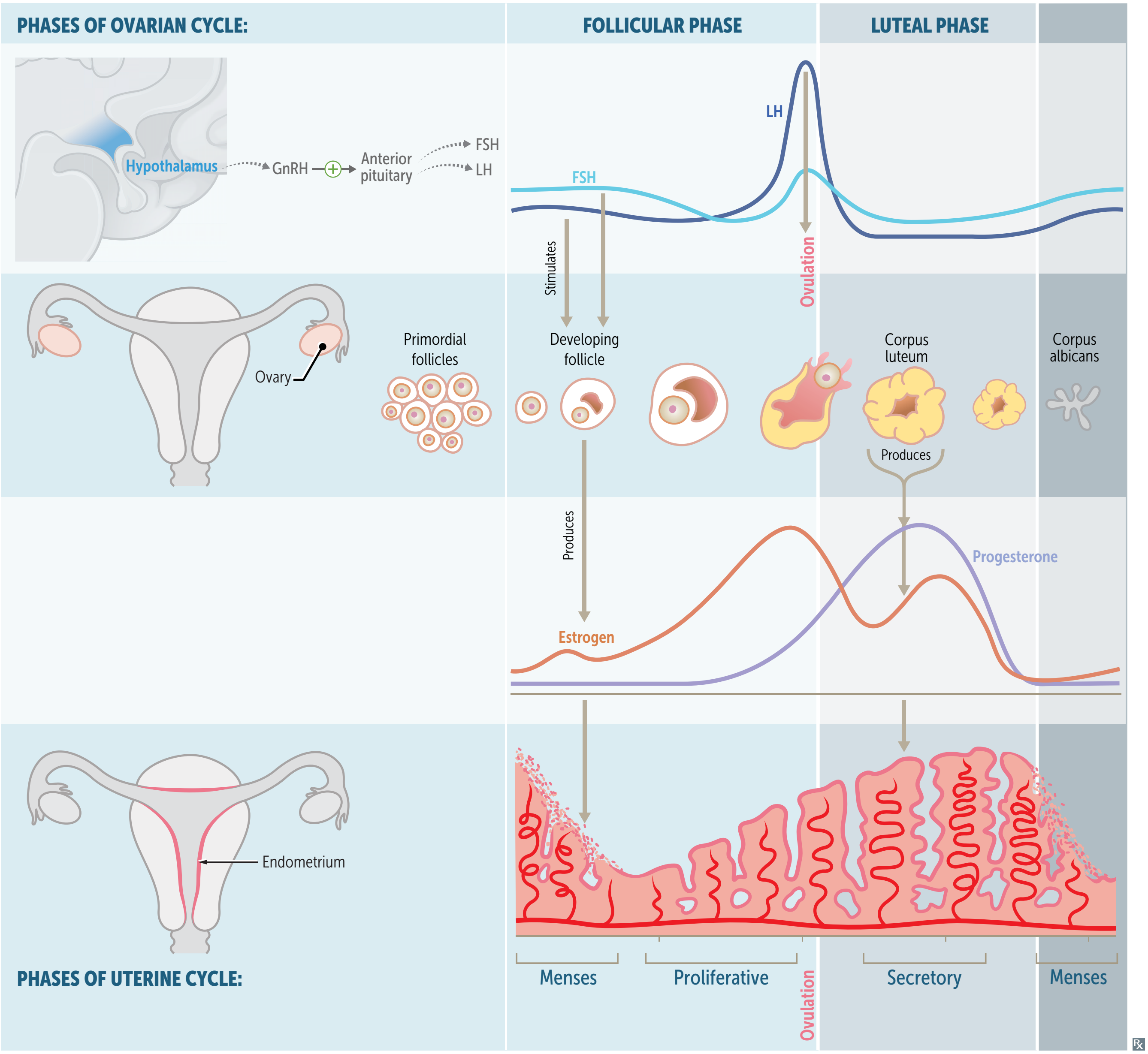
Ovulation

↑ estrogen, ↑ GnRH receptors on anterior pituitary. Estrogen surge then stimulates LH release → ovulation (rupture of follicle).

↑ temperature (progesterone induced).

Mittelschmerz—transient mid-cycle ovulatory pain (“**M**iddle hurts”); classically associated with peritoneal irritation (eg, follicular swelling/rupture, fallopian tube contraction). Can mimic appendicitis.

Menstrual cycle	Follicular phase can vary in length. Luteal phase is 14 days. Ovulation day + 14 days = menstruation. Follicular growth is fastest during 2nd week of the follicular phase. Estrogen stimulates endometrial proliferation. Progesterone maintains endometrium to support implantation. ↓ progesterone → ↓ fertility.


PHASES OF OVARIAN CYCLE:
FOLLICULAR PHASE
LUTEAL PHASE
Hypothalamus
GnRH
Anterior pituitary
FSH
LH
LH
FSH
Stimulates
Ovulation
Ovary
Primordial follicles
Developing follicle
Corpus luteum
Corpus albicans
Produces
Produces
Estrogen
Progesterone
Endometrium
PHASES OF UTERINE CYCLE:
Menses
Proliferative
Ovulation
Secretory
Menses

Pregnancy

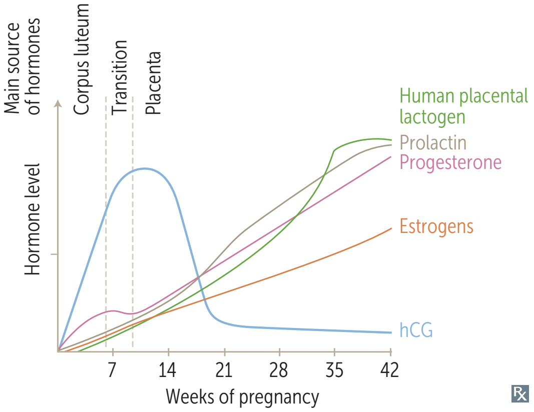
Fertilization most commonly occurs in upper end of fallopian tube (the ampulla). Occurs within 1 day of ovulation.

Implantation within the wall of the uterus occurs 6 days after fertilization. Syncytiotrophoblasts secrete hCG, which is detectable in blood 1 week after conception and on home test in urine 2 weeks after conception.

Gestational age—calculated from date of last menstrual period.

Embryonic age—calculated from date of conception (gestational age minus 2 weeks).

Physiologic adaptations in pregnancy:
- ↑ cardiac output (↑ preload, ↓ afterload, ↑ HR → ↑ placental and uterus perfusion)
- Anemia (↑↑ plasma, ↑ RBCs)
- Hypercoagulability (to ↓ blood loss at delivery)
- Hyperventilation (eliminate fetal CO_2)



Placental hormone secretion generally increases over the course of pregnancy, but hCG peaks at 8–10 weeks.

Human chorionic gonadotropin

SOURCE	Syncytiotrophoblast of placenta.
FUNCTION	Maintains corpus luteum (and thus progesterone) for first 8–10 weeks of pregnancy by acting like LH (otherwise no luteal cell stimulation → abortion). After 8–10 weeks, placenta synthesizes its own estriol and progesterone and corpus luteum degenerates. Used to detect pregnancy because it appears early in urine (see above). Has identical α subunit as LH, FSH, TSH (states of ↑ hCG can cause hyperthyroidism). β subunit is unique (pregnancy tests detect β subunit). hCG is ↑ in multiple gestations, hydatidiform moles, choriocarcinomas, and Down syndrome; hCG is ↓ in ectopic/failing pregnancy, Edward syndrome, and Patau syndrome.

Human placental lactogen (chorionic somatomammotropin)

SOURCE	Syncytiotrophoblast of placenta.
FUNCTION	Stimulates insulin production, ↑ insulin resistance due to shunting carbohydrate metabolism toward supplying glucose/amino acids to fetus. ↑ lipolysis (due to insulin resistance).

Apgar score

	Score 2	Score 1	Score 0
Appearance	 Pink	 Extremities blue	 Pale or blue
Pulse	> 100 bpm	< 100 bpm	No pulse
Grimace	Cries and pulls away	Grimaces or weak cry	No response to stimulation
Activity	 Active movement	 Arms, legs flexed	 No movement
Respiration	Strong cry	Slow, irregular	No breathing

Assessment of newborn vital signs following labor via a 10-point scale evaluated at 1 minute and 5 minutes. **Apgar** score is based on **A**ppearance, **P**ulse, **G**rimace, **A**ctivity, and **R**espiration.

Apgar scores < 7 require further evaluation. If Apgar score remains low at later time points, there is ↑ risk the child will develop long-term neurologic damage.

Low birth weight

Defined as < 2500 g. Caused by prematurity or intrauterine growth restriction (IUGR). Associated with ↑ risk of sudden infant death syndrome (SIDS) and with ↑ overall mortality. Other problems include impaired thermoregulation and immune function, hypoglycemia, polycythemia, and impaired neurocognitive/emotional development. Complications include infections, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and persistent fetal circulation.

Lactation

After labor, the ↓ in progesterone and estrogen disinhibits lactation. Suckling is required to maintain milk production, since ↑ nerve stimulation → ↑ oxytocin and prolactin.

Prolactin—induces and maintains lactation and ↓ reproductive function.

Oxytocin—assists in milk letdown; also promotes uterine contractions.

Breast milk is the ideal nutrition for infants < 6 months old. Contains maternal immunoglobulins (conferring passive immunity; mostly IgA), macrophages, lymphocytes. Breast milk reduces infant infections and is associated with ↓ risk for child to develop asthma, allergies, diabetes mellitus, and obesity. Exclusively breastfed infants require vitamin D supplementation.

Breastfeeding ↓ maternal risk of breast and ovarian cancer and facilitates mother-child bonding.

Menopause

Diagnosed by amenorrhea for 12 months. ↓ estrogen production due to age-linked decline in number of ovarian follicles. Average age at onset is 51 years (earlier in smokers).

Usually preceded by 4–5 years of abnormal menstrual cycles. Source of estrogen (estrone) after menopause becomes peripheral conversion of androgens, ↑ androgens → hirsutism.

↑↑ FSH is specific for menopause (loss of negative feedback on FSH due to ↓ estrogen).

Hormonal changes: ↓ estrogen, ↑↑ FSH, ↑ LH (no surge), ↑ GnRH.

Causes **HAVOCS**: **H**ot flashes, **A**trophy of the **V**agina, **O**steoporosis, **C**oronary artery disease, **S**leep disturbances.

Menopause before age 40 suggests 1° ovarian insufficiency (premature ovarian failure).

Androgens

Testosterone, dihydrotestosterone (DHT), androstenedione.

SOURCE

DHT and testosterone (testis), **A**n**D**rostenedione (**AD**renal)

Potency: DHT > testosterone > androstenedione.

FUNCTION

Testosterone:

- Differentiation of epididymis, vas deferens, seminal vesicles (internal genitalia, except prostate).
- Growth spurt: penis, seminal vesicles, sperm, muscle, RBCs.
- Deepening of voice.
- Closing of epiphyseal plates (via estrogen converted from testosterone).
- Libido.

DHT:

- Early—differentiation of penis, scrotum, prostate.
- Late—prostate growth, balding, sebaceous gland activity.

Testosterone is converted to DHT by 5α-reductase, which is inhibited by finasteride.

In the male, androgens are converted to estrogen by cytochrome P-450 aromatase (primarily in adipose tissue and testis).

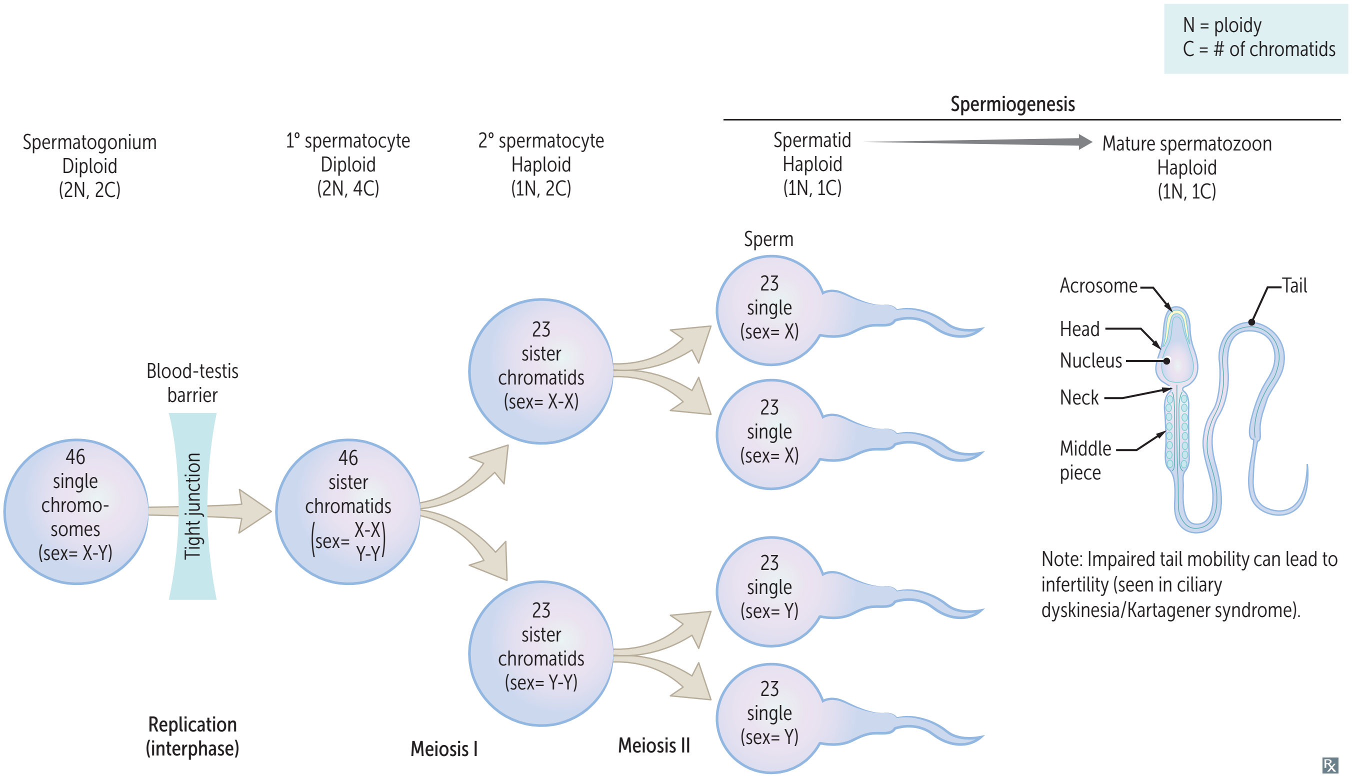
Aromatase is the key enzyme in conversion of androgens to estrogen.

Exogenous testosterone → inhibition of hypothalamic–pituitary–gonadal axis → ↓ intratesticular testosterone → ↓ testicular size → azoospermia.

Spermatogenesis

Spermatogenesis begins at puberty with spermatogonia. Full development takes 2 months. Occurs in seminiferous tubules. Produces spermatids that undergo spermiogenesis (loss of cytoplasmic contents, gain of acrosomal cap) to form mature spermatozoon.

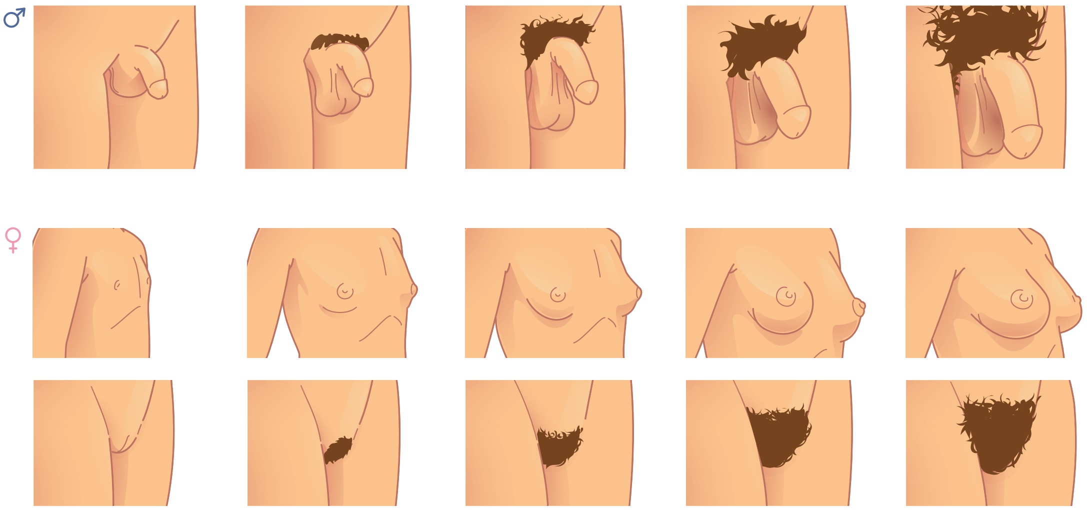
"**Gonium**" is **going** to be a sperm; "**Z**oon" is "**Z**ooming" to egg.


N = ploidy
C = # of chromatids
Spermiogenesis
Spermatogonium
Diploid
(2N, 2C)
1° spermatocyte
Diploid
(2N, 4C)
2° spermatocyte
Haploid
(1N, 2C)
Spermatid
Haploid
(1N, 1C)
Mature spermatozoon
Haploid
(1N, 1C)
Sperm
Blood-testis barrier
Tight junction
46 single chromo-somes (sex= X-Y)
46 sister chromatids (sex= X-X Y-Y)
23 sister chromatids (sex= X-X)
23 sister chromatids (sex= Y-Y)
23 single (sex= X)
23 single (sex= X)
23 single (sex= Y)
23 single (sex= Y)
Acrosome
Head
Nucleus
Neck
Middle piece
Tail
Replication (interphase)
Meiosis I
Meiosis II

Note: Impaired tail mobility can lead to infertility (seen in ciliary dyskinesia/Kartagener syndrome).

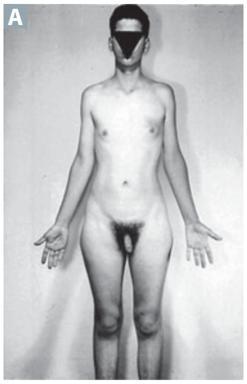
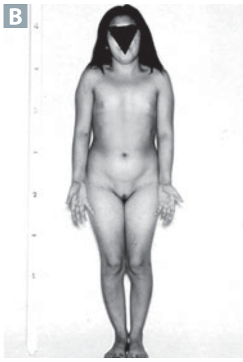
Tanner stages of sexual development

Tanner stage is assigned independently to genitalia, pubic hair, and breast (eg, a person can have Tanner stage 2 genitalia, Tanner stage 3 pubic hair).



Stage I	Stage II	Stage III	Stage IV	Stage V
No sexual hair ♂ ♀ Flat-appearing chest with raised nipple ♀	Pubic hair appears ♂ ♀ (pubarche) Testicular enlargement ♂ Breast bud forms ♀ (thelarche)	Coarsening of pubic hair ♂ ♀ Penis size/length ↑ ♂ Breast enlarges, mound forms ♀	Coarse hair across pubis, sparing thigh ♂ ♀ Penis width/glans ↑ ♂ Breast enlarges, raised areola, mound on mound ♀	Coarse hair across pubis and medial thigh ♂ ♀ Penis and testis enlarge to adult size ♂ Adult breast contour, areola flattens ♀
Pre-pubertal	~ 10–11.5 years	~ 11.5–13 years	~ 13–15 years	Usually > 15 years

▶ REPRODUCTIVE—PATHOLOGY

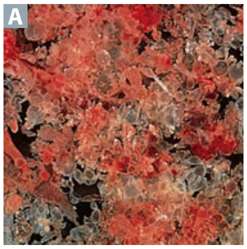
Sex chromosome disorders	Aneuploidy most commonly due to meiotic nondisjunction.	
Klinefelter syndrome [male] (47,XXY) 	Testicular atrophy, eunuchoid body shape, tall, long extremities, gynecomastia, female hair distribution A. May present with developmental delay. Presence of inactivated X chromosome (Barr body). Common cause of hypogonadism seen in infertility work-up.	Dysgenesis of seminiferous tubules → ↓ inhibin B → ↑ FSH. Abnormal Leydig cell function → ↓ testosterone → ↑ LH → ↑ estrogen.
Turner syndrome [female] (45,XO) 	Short stature (if untreated; preventable with growth hormone therapy), ovarian dysgenesis (streak ovary), shield chest B, bicuspid aortic valve, coarctation (femoral < brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney B. Most common cause of 1° amenorrhea. No Barr body.	Menopause before menarche. ↓ estrogen leads to ↑ LH, FSH. Sometimes due to mitotic error → mosaicism (eg, 45,XO/46,XX). Pregnancy is possible in some cases (IVF, exogenous estradiol-17β and progesterone).
Double Y males (XYY)	Phenotypically normal (usually undiagnosed), very tall. Normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders.	
Ovotesticular disorder of sex development	46,XX > 46,XY. Both ovarian and testicular tissue present (ovotestis); ambiguous genitalia. Previously called true hermaphroditism.	

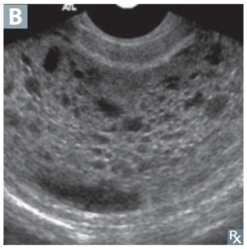
Diagnosing disorders of sex hormones

Testosterone	LH	Diagnosis
↑	↑	Defective androgen receptor
↑	↓	Testosterone-secreting tumor, exogenous steroids
↓	↑	Hypergonadotrophic hypogonadism (1°)
↓	↓	Hypogonadotropic hypogonadism (2°)

Other disorders of sex development	Disagreement between the phenotypic sex (external genitalia, influenced by hormonal levels) and the gonadal sex (testes vs ovaries, corresponds with Y chromosome). Includes the terms pseudohermaphrodite, hermaphrodite, and intersex.
46,XX DSD	Ovaries present, but external genitalia are virilized or ambiguous. Due to excessive and inappropriate exposure to androgenic steroids during early gestation (eg, congenital adrenal hyperplasia or exogenous administration of androgens during pregnancy).
46,XY DSD	Testes present, but external genitalia are female or ambiguous. Most common form is androgen insensitivity syndrome (testicular feminization).
Placental aromatase deficiency	Inability to synthesize estrogens from androgens. Masculinization of female (46,XX DSD) infants (ambiguous genitalia), ↑ serum testosterone and androstenedione. Can present with maternal virilization during pregnancy (fetal androgens cross the placenta).
Androgen insensitivity syndrome	Defect in androgen receptor resulting in normal-appearing female (46,XY DSD); female external genitalia with scant axillary and pubic (sexual) hair, rudimentary vagina; uterus and fallopian tubes absent. Patients develop normal functioning testes (often found in labia majora; surgically removed to prevent malignancy). ↑ testosterone, estrogen, LH (vs sex chromosome disorders).
5α-reductase deficiency	Autosomal recessive; sex limited to genetic males (46,XY DSD). Inability to convert testosterone to DHT. Ambiguous genitalia until puberty, when ↑ testosterone causes masculinization/↑ growth of external genitalia. Testosterone/estrogen levels are normal; LH is normal or ↑. Internal genitalia are normal.
Kallmann syndrome	Failure to complete puberty; a form of hypogonadotropic hypogonadism. Defective migration of GnRH-releasing neurons and subsequent failure of GnRH-releasing olfactory bulbs to develop → ↓ synthesis of GnRH in the hypothalamus; anosmia; ↓ GnRH, FSH, LH, testosterone. Infertility (low sperm count in males; amenorrhea in females).

Hydatidiform mole



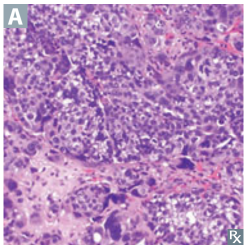


Cystic swelling of chorionic villi and proliferation of chorionic epithelium (only trophoblast). Presents with vaginal bleeding, uterine enlargement more than expected, pelvic pressure/pain. Associated with hCG-mediated sequelae: early preeclampsia (before 20 weeks), theca-lutein cysts, hyperemesis gravidarum, hyperthyroidism.

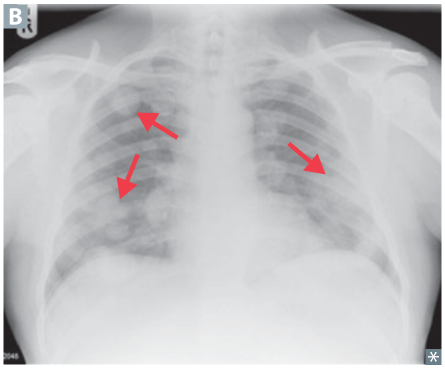
Treatment: dilation and curettage and methotrexate. Monitor β-hCG.

	Complete mole	Partial mole
KARYOTYPE	46,XX; 46,XY	69,XXX; 69,XXY; 69,XYY
COMPONENTS	Most commonly enucleated egg + single sperm (subsequently duplicates paternal DNA)	2 sperm + 1 egg
FETAL PARTS	No	Yes (partial = fetal parts)
UTERINE SIZE	↑	—
hCG	↑↑↑↑	↑
IMAGING	“Honeycombed” uterus or “clusters of grapes” A, “snowstorm” on ultrasound B	Fetal parts
RISK OF MALIGNANCY (GESTATIONAL TROPHOBLASTIC NEOPLASIA)	15–20%	< 5%
RISK OF CHORIOCARCINOMA	2%	Rare

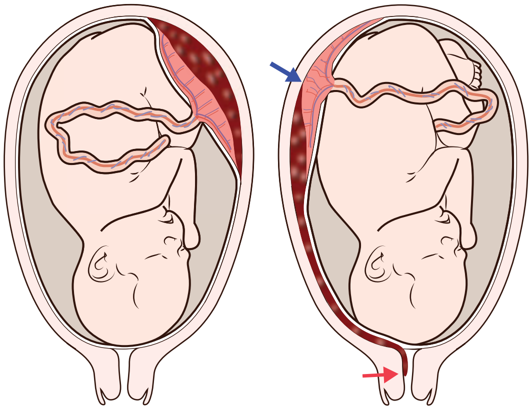
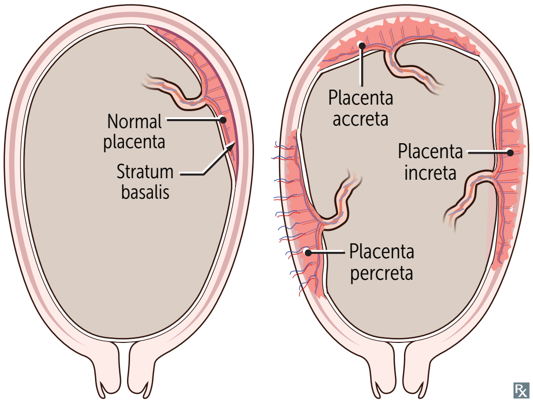
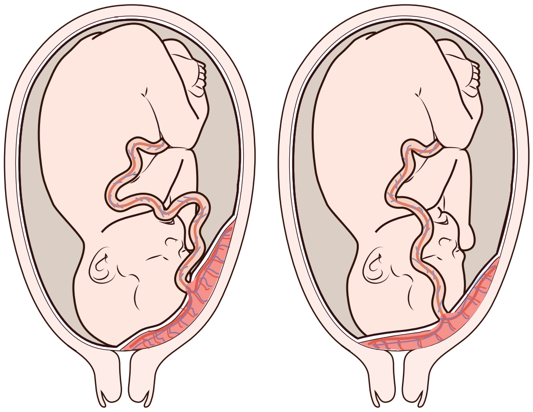
Choriocarcinoma



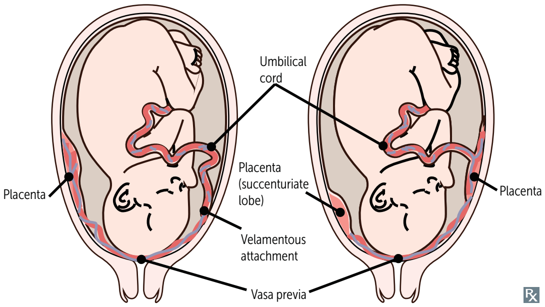
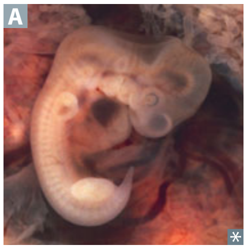
Rare; can develop during or after pregnancy in mother or baby. Malignancy of trophoblastic tissue A (cytotrophoblasts, syncytiotrophoblasts); **no** chorionic villi present. ↑ frequency of bilateral/multiple theca-lutein cysts. Presents with abnormal ↑ β-hCG, shortness of breath, hemoptysis. Hematogenous spread to lungs → “cannonball” metastases B.



Pregnancy complications

Placental abruption (abruptio placentae)	Premature separation (partial or complete) of placenta from uterine wall before delivery of infant. Risk factors: trauma (eg, motor vehicle accident), smoking, hypertension, preeclampsia, cocaine abuse. Presentation: **abrupt**, painful bleeding (concealed or apparent) in third trimester; possible DIC, maternal shock, fetal distress. Life threatening for mother and fetus.	 Complete abruption with concealed hemorrhage Partial abruption (blue arrow) with apparent hemorrhage (red arrow)
Placenta accreta/ increta/percreta	Defective decidual layer → abnormal attachment and separation after delivery. Risk factors: prior C-section, inflammation, placenta previa. Three types distinguishable by the depth of penetration: Placenta accreta—placenta **attaches** to myometrium without penetrating it; most common type. Placenta increta—placenta penetrates **into** myometrium. Placenta percreta—placenta penetrates (“**perforates**”) through myometrium and into uterine serosa (invades entire uterine wall); can result in placental attachment to rectum or bladder. Presentation: often detected on ultrasound prior to delivery. No separation of placenta after delivery → postpartum bleeding (can cause Sheehan syndrome).	 Normal placenta Stratum basalis Placenta accreta Placenta increta Placenta percreta
Placenta previa	Attachment of placenta to lower uterine segment over (or < 2 cm from) internal cervical os. Risk factors: multiparity, prior C-section. Associated with painless third-trimester bleeding.	 Partial placenta previa Complete placenta previa

Pregnancy complications *(continued)*

Vasa previa	Fetal vessels run over, or in close proximity to, cervical os. May result in vessel rupture, exsanguination, fetal death. Presents with triad of membrane rupture, painless vaginal bleeding, fetal bradycardia (< 110 beats/min). Emergency C-section usually indicated. Frequently associated with velamentous umbilical cord insertion (cord inserts in chorioamniotic membrane rather than placenta → fetal vessels travel to placenta unprotected by Wharton jelly).	 Umbilical cord Placenta Placenta (succenturiate lobe) Velamentous attachment Placenta Vasa previa
Postpartum hemorrhage	Due to 4 T's: **T**one (uterine atony; most common), **T**rauma (lacerations, incisions, uterine rupture), **T**hrombin (coagulopathy), **T**issue (retained products of conception).	
Ectopic pregnancy 	Most often in ampulla of fallopian tube (A shows 10-mm embryo in oviduct at 7 weeks of gestation). Suspect with history of amenorrhea, lower-than-expected rise in hCG based on dates, and sudden lower abdominal pain; confirm with ultrasound. Often clinically mistaken for appendicitis.	Pain +/– bleeding. Risk factors: ▪ Prior ectopic pregnancy ▪ History of infertility ▪ Salpingitis (PID) ▪ Ruptured appendix ▪ Prior tubal surgery

Amniotic fluid abnormalities

Polyhydramnios	Too much amniotic fluid; associated with fetal malformations (eg, esophageal/duodenal atresia, anencephaly; both result in inability to swallow amniotic fluid), maternal diabetes, fetal anemia, multiple gestations.
Oligohydramnios	Too little amniotic fluid; associated with placental insufficiency, bilateral renal agenesis, posterior urethral valves (in males) and resultant inability to excrete urine. Any profound oligohydramnios can cause Potter sequence.

Hypertension in pregnancy

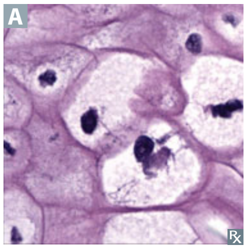
Gestational hypertension (pregnancy-induced hypertension)	BP > 140/90 mm Hg after 20th week of gestation. No pre-existing hypertension. No proteinuria or end-organ damage.	Treatment: antihypertensives (**H**ydralazine, α-**M**ethyldopa, **L**abetalol, **N**ifedipine), deliver at 37–39 weeks. **H**ypertensive **M**oms **L**ove **N**ifedipine.
Preeclampsia	New-onset hypertension with either proteinuria or end-organ dysfunction after 20th week of gestation (< 20 weeks suggests molar pregnancy). Caused by abnormal placental spiral arteries → endothelial dysfunction, vasoconstriction, ischemia. Incidence ↑ in patients with pre-existing hypertension, diabetes, chronic renal disease, autoimmune disorders (eg, thrombophilias such as anticoagulant and anticardiolipin antibodies). Complications: placental abruption, coagulopathy, renal failure, uteroplacental insufficiency; may lead to eclampsia (+ seizures) and/or HELLP syndrome.	Treatment: antihypertensives, IV magnesium sulfate (to prevent seizure); definitive is delivery of fetus.
Eclampsia	Preeclampsia + maternal seizures. Maternal death due to stroke, intracranial hemorrhage, or ARDS.	Treatment: IV magnesium sulfate, antihypertensives, immediate delivery.
HELLP syndrome	**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets. A manifestation of severe preeclampsia. Blood smear shows schistocytes. Can lead to hepatic subcapsular hematomas → rupture → severe hypotension.	Treatment: immediate delivery.

Gynecologic tumor epidemiology	Incidence (US)—endometrial > ovarian > cervical; cervical cancer is more common worldwide due to lack of screening or HPV vaccination. Worst prognosis—ovarian > endometrial > cervical.

Vaginal tumors

Squamous cell carcinoma	Usually 2° to cervical SCC; 1° vaginal carcinoma rare.
Clear cell adenocarcinoma	Affects women who had exposure to DES in utero.
Sarcoma botryoides	Embryonal rhabdomyosarcoma variant. Affects girls < 4 years old; spindle-shaped cells; desmin ⊕. Presents with clear, grape-like, polypoid mass emerging from vagina.

Cervical pathology

Dysplasia and carcinoma in situ 	Disordered epithelial growth; begins at basal layer of squamocolumnar junction (transformation zone) and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (severe, irreversible dysplasia or carcinoma in situ), depending on extent of dysplasia. Associated with HPV-16 and HPV-18, which produce both the E6 gene product (inhibits *p53* suppressor gene) and E7 gene product (inhibits *RB* suppressor gene); koilocytes A are pathognomonic of HPV infection. May progress slowly to invasive carcinoma if left untreated. Typically asymptomatic (detected with Pap smear) or presents as abnormal vaginal bleeding (often postcoital). Risk factors: multiple sexual partners (#1), smoking, starting sexual intercourse at young age, HIV infection.
Invasive carcinoma	Often squamous cell carcinoma. Pap smear can detect cervical dysplasia before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters → renal failure.

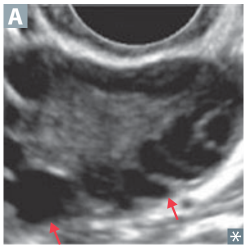
Premature ovarian failure

	Premature atresia of ovarian follicles in women of reproductive age. Patients present with signs of menopause after puberty but before age 40.	↓ estrogen, ↑ LH, ↑ FSH.

Most common causes of anovulation

Pregnancy, polycystic ovarian syndrome, obesity, HPO axis abnormalities, premature ovarian failure, hyperprolactinemia, thyroid disorders, eating disorders, competitive athletics, Cushing syndrome, adrenal insufficiency.

Polycystic ovarian syndrome (Stein-Leventhal syndrome)



Hyperinsulinemia and/or insulin resistance hypothesized to alter hypothalamic hormonal feedback response → ↑ LH:FSH, ↑ androgens (eg, testosterone) from theca interna cells, ↓ rate of follicular maturation → unruptured follicles (cysts) + anovulation. Common cause of subfertility in women.

Enlarged, bilateral cystic ovaries A; presents with amenorrhea/oligomenorrhea, hirsutism, acne, ↓ fertility. Associated with obesity. ↑ risk of endometrial cancer 2° to unopposed estrogen from repeated anovulatory cycles.

Treatment: cycle control via weight reduction (↓ peripheral estrone formation), OCPs (prevent endometrial hyperplasia due to unopposed estrogen); clomiphene, metformin to induce ovulation; spironolactone, ketoconazole (antiandrogens) to treat hirsutism.

Ovarian cysts

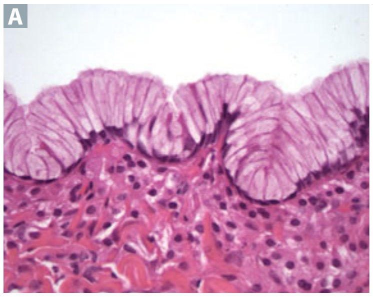
Follicular cyst	Distention of unruptured graafian follicle. May be associated with hyperestrogenism, endometrial hyperplasia. Most common ovarian mass in young women.
Theca-lutein cyst	Often bilateral/multiple. Due to gonadotropin stimulation. Associated with choriocarcinoma and hydatidiform moles.

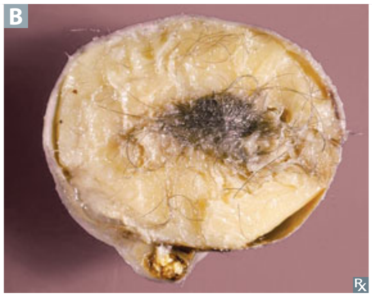
Ovarian neoplasms

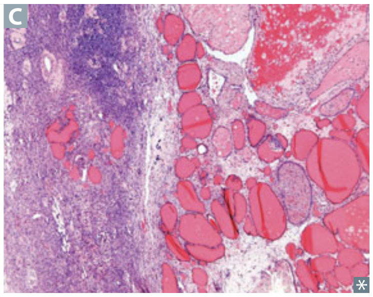
Most common adnexal mass in women > 55 years old. Can be benign or malignant. Arise from surface epithelium, germ cells, or sex cord stromal tissue.

Majority of malignant tumors are epithelial (serous cystadenocarcinoma most common). Risk ↑ with advanced age, infertility, endometriosis, PCOS, genetic predisposition (*BRCA-1* or *BRCA-2* mutation, Lynch syndrome, strong family history). Risk ↓ with previous pregnancy, history of breastfeeding, OCPs, tubal ligation. Presents with adnexal mass, abdominal distension, bowel obstruction, pleural effusion. Monitor response to therapy/relapse by measuring CA 125 levels (not good for screening).

Benign ovarian neoplasms	
Serous cystadenoma	Most common ovarian neoplasm. Lined with fallopian tube–like epithelium. Often bilateral.
Mucinous cystadenoma	Multiloculated, large. Lined by mucus-secreting epithelium A.
Endometrioma	Endometriosis (ectopic endometrium-like tissue) within ovary with cyst formation. Presents with pelvic pain, dysmenorrhea, dyspareunia; symptoms may vary with menstrual cycle. "Chocolate cyst"—endometrioma filled with dark, reddish-brown blood. Complex mass on ultrasound.
Mature cystic teratoma (dermoid cyst)	Germ cell tumor, most common ovarian tumor in females 10–30 years old. Cystic mass containing elements from all 3 germ layers (eg, teeth, hair, sebum) B. Can present with pain 2° to ovarian enlargement or torsion. A monodermal form with thyroid tissue (struma ovarii) uncommonly presents with hyperthyroidism C.
Brenner tumor	Looks like bladder. Solid tumor that is pale yellow-tan and appears encapsulated. "Coffee bean" nuclei on H&E stain.
Fibromas	Bundles of spindle-shaped fibroblasts. Meigs syndrome—triad of ovarian fibroma, ascites, hydrothorax. "Pulling" sensation in groin.
Thecoma	Like granulosa cell tumors, may produce estrogen. Usually presents as abnormal uterine bleeding in a postmenopausal woman.

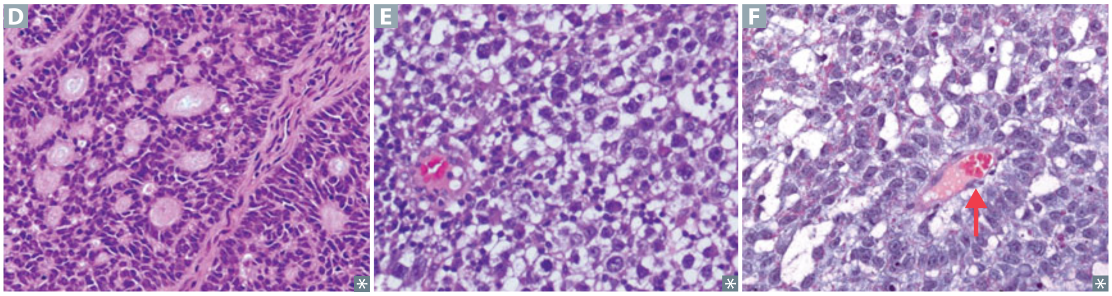






Ovarian neoplasms *(continued)*

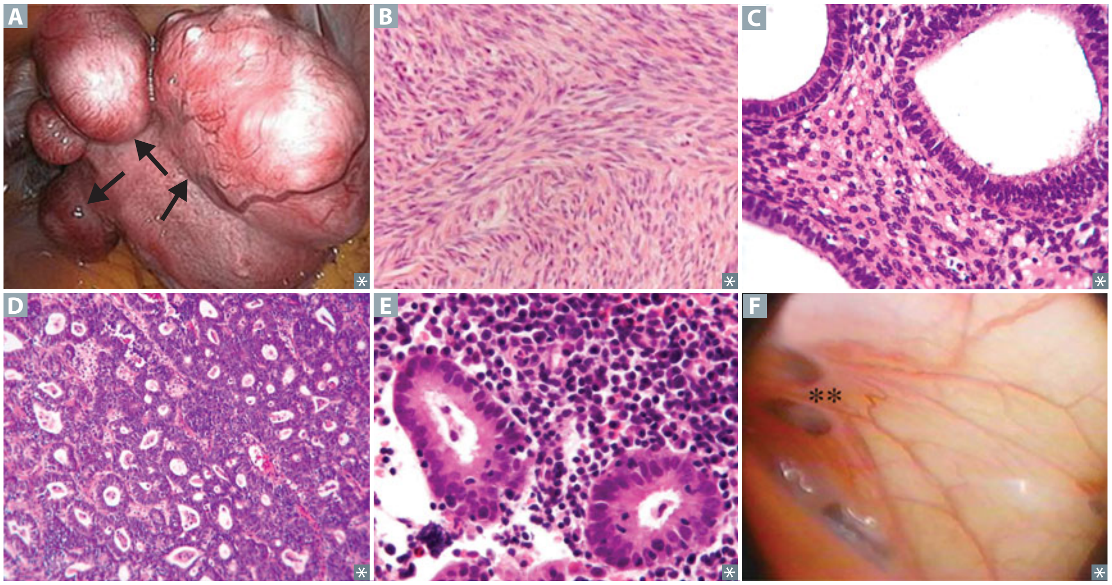
Malignant ovarian neoplasms	
Granulosa cell tumor	Most common malignant stromal tumor. Predominantly women in their 50s. Often produces estrogen and/or progesterone and presents with postmenopausal bleeding, sexual precocity (in pre-adolescents), breast tenderness. Histology shows Call-Exner bodies D (granulosa cells arranged haphazardly around collections of eosinophilic fluid, resembling primordial follicles).
Serous cystadenocarcinoma	Most common malignant ovarian neoplasm, frequently bilateral. Psammoma bodies.
Mucinous cystadenocarcinoma	Pseudomyxoma peritonei–intraperitoneal accumulation of mucinous material from ovarian or appendiceal tumor.
Immature teratoma	Aggressive, contains fetal tissue, neuroectoderm. Commonly diagnosed before age 20. Typically represented by immature/embryonic-like neural tissue.
Dysgerminoma	Most common in adolescents. Equivalent to male seminoma but rarer. 1% of all ovarian tumors; 30% of germ cell tumors. Sheets of uniform "fried egg" cells E. hCG, LDH = tumor markers.
Yolk sac (endodermal sinus) tumor	Aggressive, in ovaries or testes and sacrococcygeal area in young children. Most common tumor in male infants. Yellow, friable (hemorrhagic), solid mass. 50% have Schiller-Duval bodies (resemble glomeruli) F. AFP = tumor marker.
Krukenberg tumor	GI malignancy that metastasizes to ovaries → mucin-secreting signet cell adenocarcinoma.



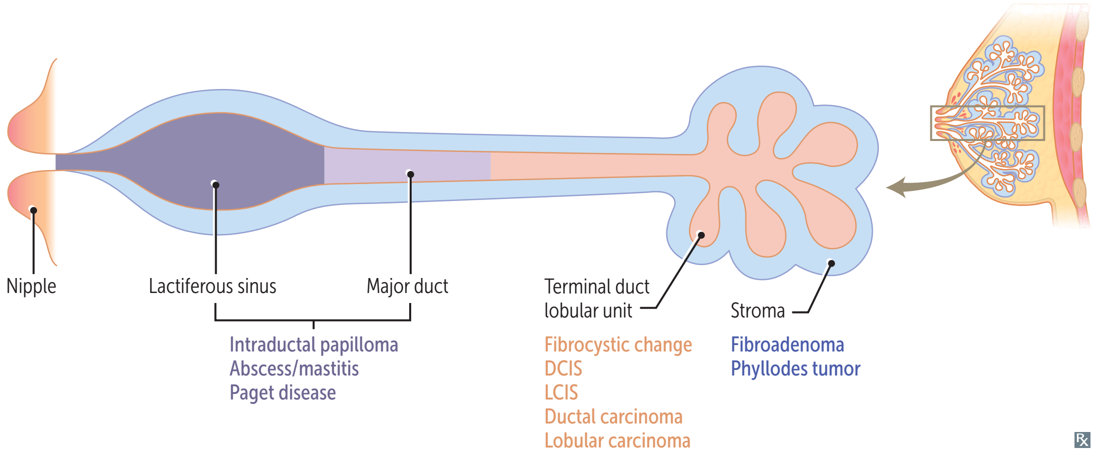
Endometrial conditions	**PALM-COEIN**: **P**olyp, **A**denomyosis, **L**eiomyoma, **M**alignancy and hyperplasia, **C**oagulopathy, **O**vulatory dysfunction, **E**ndometrial, **I**atrogenic, and **N**ot otherwise classified.
Polyp	Well-circumscribed collection of endometrial tissue within uterine wall. May contain smooth muscle cells. Can extend into endometrial cavity in the form of a polyp. May be asymptomatic or present with painless abnormal uterine bleeding.
Adenomyosis	Extension of endometrial tissue (glandular) into uterine myometrium. Caused by hyperplasia of basal layer of endometrium. Presents with dysmenorrhea, menorrhagia, uniformly enlarged, soft, globular uterus. Treatment: GnRH agonists, hysterectomy or excision of an organized adenomyoma.
Asherman syndrome	Adhesions and/or fibrosis of the endometrium. Often associated with dilation and curettage of intrauterine cavity.
Leiomyoma (fibroid)	Most common tumor in females. Often presents with multiple discrete tumors A. ↑ incidence in African Americans. Benign smooth muscle tumor; malignant transformation to leiomyosarcoma is rare. Estrogen sensitive—tumor size ↑ with pregnancy and ↓ with menopause. Peak occurrence at 20–40 years old. May be asymptomatic, cause abnormal uterine bleeding, or result in miscarriage. Severe bleeding may lead to iron deficiency anemia. Whorled pattern of smooth muscle bundles with well-demarcated borders B.
Endometrial hyperplasia	Abnormal endometrial gland proliferation C usually caused by excess estrogen stimulation. ↑ risk for endometrial carcinoma; nuclear atypia is greater risk factor than complex (vs simple) architecture. Presents as postmenopausal vaginal bleeding. Risk factors include anovulatory cycles, hormone replacement therapy, polycystic ovarian syndrome, granulosa cell tumor.
Endometrial carcinoma	Most common gynecologic malignancy D. Peak occurrence at 55–65 years old. Presents with vaginal bleeding. Typically preceded by endometrial hyperplasia. Risk factors include prolonged use of estrogen without progestins, obesity, diabetes, hypertension, nulliparity, late menopause, early menarche, Lynch syndrome.
Endometritis	Inflammation of endometrium E associated with retained products of conception following delivery, miscarriage, abortion, or with foreign body (eg, IUD). Retained material in uterus promotes infection by bacterial flora from vagina or intestinal tract. Treatment: gentamicin + clindamycin +/– ampicillin.

Endometrial conditions *(continued)*

Endometriosis	Non-neoplastic endometrium-like glands/stroma outside endometrial cavity. Can be found anywhere; most common sites are ovary (frequently bilateral), pelvis, peritoneum. In ovary, appears as endometrioma (blood-filled “chocolate cysts” [oval structures above and below asterisks in F]). May be due to retrograde flow, metaplastic transformation of multipotent cells, transportation of endometrial tissue via lymphatic system. Characterized by cyclic pelvic pain, bleeding, dysmenorrhea, dyspareunia, dyschezia (pain with defecation), infertility; normal-sized uterus. Treatment: NSAIDs, OCPs, progestins, GnRH agonists, danazol, laparoscopic removal.

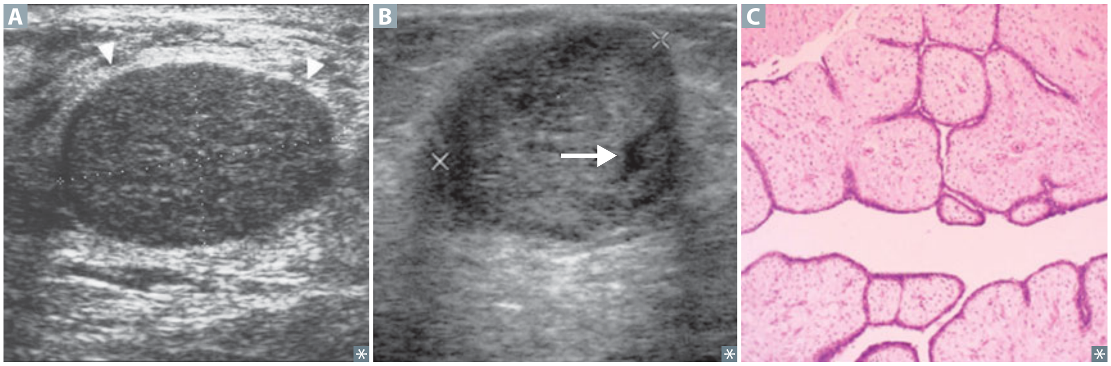


Breast pathology


Nipple
Lactiferous sinus
Major duct
Terminal duct lobular unit
Stroma
Intraductal papilloma
Abscess/mastitis
Paget disease
Fibrocystic change
DCIS
LCIS
Ductal carcinoma
Lobular carcinoma
Fibroadenoma
Phyllodes tumor

Benign breast disease

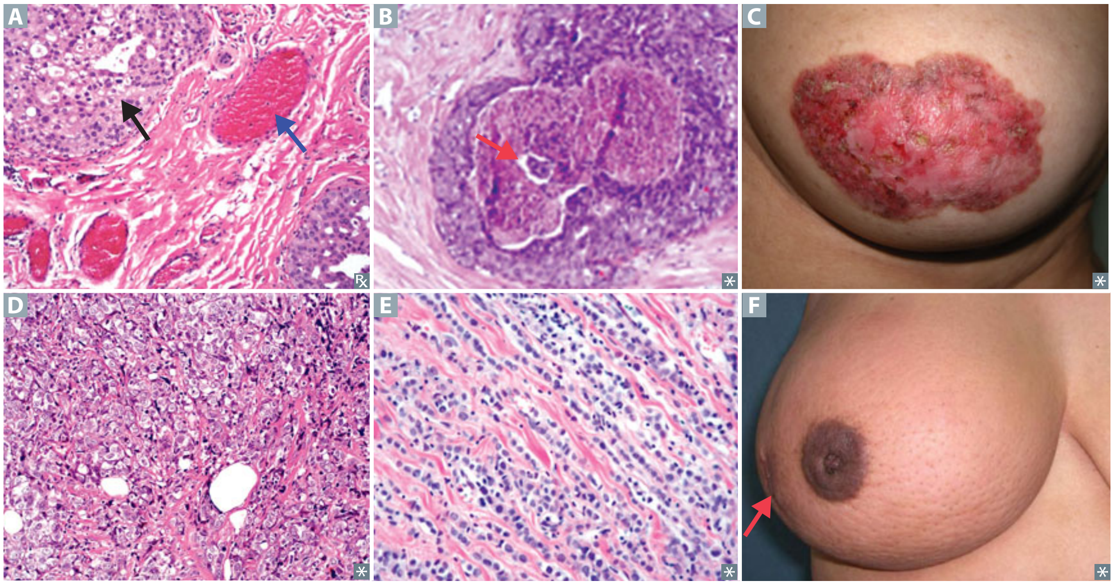
Fibrocystic changes	Most common in premenopausal women > 35 years old. Present with premenstrual breast pain or lumps; often bilateral and multifocal. Nonproliferative lesions include simple cysts (fluid-filled duct dilation, blue dome), papillary apocrine change/metaplasia, stromal fibrosis. Risk of cancer is usually not increased. Subtypes include: ▪ Sclerosing adenosis—acini and stromal fibrosis, associated with calcifications. Slight (1.5–2 ×) ↑ risk for cancer. ▪ Epithelial hyperplasia—cells in terminal ductal or lobular epithelium. ↑ risk of carcinoma with atypical cells.
Inflammatory processes	Fat necrosis—benign, usually painless, lump due to injury to breast tissue. Calcified oil cyst on mammography; necrotic fat and giant cells on biopsy. Up to 50% of patients may not report trauma. Lactational mastitis—occurs during breastfeeding, ↑ risk of bacterial infection through cracks in nipple. S *aureus* is most common pathogen. Treat with antibiotics and continue breastfeeding.
Benign tumors	Fibroadenoma—most common in women < 35 years old. Small, well-defined, mobile mass A. ↑ size and tenderness with ↑ estrogen (eg, pregnancy, prior to menstruation). Risk of cancer is usually not increased. Intraductal papilloma—small papillary tumor within lactiferous ducts, typically beneath areola. Most common cause of nipple discharge (serous or bloody). Slight (1.5–2 ×) ↑ risk for cancer. Phyllodes tumor—large mass B of connective tissue and cysts with "leaf-like" lobulations C. Most common in 5th decade. Some may become malignant.
Gynecomastia	Breast enlargement in males due to ↑ estrogen compared with androgen activity. Physiologic (not pathologic) in newborn, pubertal, and elderly males, but may persist after puberty. Other causes include cirrhosis, hypogonadism (eg, Klinefelter syndrome), testicular tumors, and drugs (**S**pironolactone, **H**ormones, **C**imetidine, **K**etoconazole: "**S**ome **H**ormones **C**reate **K**nockers").



Malignant breast tumors	Commonly postmenopausal. Usually arise from terminal duct lobular unit. Amplification/overexpression of estrogen/progesterone receptors or *c-erbB2* (HER-2, an EGF receptor) is common; triple negative (ER ⊖, PR ⊖, and Her2/Neu ⊖) more aggressive; type affects therapy and prognosis. Axillary lymph node involvement indicating metastasis is the most important prognostic factor in early-stage disease. Most often located in upper-outer quadrant of breast.	Risk factors: ↑ estrogen exposure, ↑ total number of menstrual cycles, older age at 1st live birth, obesity (↑ estrogen exposure as adipose tissue converts androstenedione to estrone), *BRCA1* or *BRCA2* gene mutations, African American ethnicity (↑ risk for triple ⊖ breast cancer).

TYPE	CHARACTERISTICS	NOTES
Noninvasive		
Ductal carcinoma in situ	Fills ductal lumen (black arrow in A indicates neoplastic cells in duct; blue arrow shows engorged blood vessel). Arises from ductal atypia. Often seen early as microcalcifications on mammography.	Early malignancy without basement membrane penetration.
Comedocarcinoma	Ductal, central necrosis (arrow in B). Subtype of DCIS.	
Paget disease	Results from underlying DCIS or invasive breast cancer. Eczematous patches on nipple C. Paget cells = intraepithelial adenocarcinoma cells.	
Invasive		
Invasive ductal carcinoma	Firm, fibrous, "rock-hard" mass with sharp margins and small, glandular, duct-like cells D. Tumor can deform suspensory ligaments → dimpling of skin. Classic morphology: "stellate" infiltration.	Most common (~ 75% of all breast cancers).
Invasive lobular carcinoma	Orderly row of cells ("single file" E), due to ↓ E-cadherin expression.	Often bilateral with multiple lesions in the same location. Lines of cells = Lobular.
Medullary carcinoma	Fleshy, cellular, lymphocytic infiltrate.	Good prognosis.
Inflammatory breast cancer	Dermal lymphatic invasion by breast carcinoma. Peau d'orange (breast skin resembles orange peel F); neoplastic cells block lymphatic drainage.	Poor prognosis (50% survival at 5 years). Often mistaken for mastitis or Paget disease.

Malignant breast tumors *(continued)*

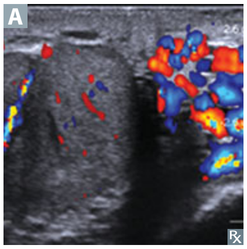


Penile pathology

Peyronie disease	Abnormal curvature of penis due to fibrous plaque within tunica albuginea. Associated with erectile dysfunction. Can cause pain, anxiety. Consider surgical repair once curvature stabilizes. Distinct from penile fracture (rupture of corpora cavernosa due to forced bending).
Ischemic priapism	Painful sustained erection lasting > 4 hours. Associated with sickle cell disease (sickled RBCs block venous drainage of corpus cavernosum vascular channels), medications (eg, sildenafil, trazodone). Treat immediately with corporal aspiration, intracavernosal phenylephrine, or surgical decompression to prevent ischemia.
Squamous cell carcinoma	More common in Asia, Africa, South America. Precursor in situ lesions: Bowen disease (in penile shaft, presents as leukoplakia), erythroplasia of Queyrat (cancer of glans, presents as erythroplakia), Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with uncircumcised males and HPV.

Cryptorchidism	Undescended testis (one or both); impaired spermatogenesis (since sperm develop best at temperatures < 37°C); can have normal testosterone levels (Leydig cells are mostly unaffected by temperature); associated with ↑ risk of germ cell tumors. Prematurity ↑ risk of cryptorchidism. ↓ inhibin B, ↑ FSH, ↑ LH; testosterone ↓ in bilateral cryptorchidism, normal in unilateral.

Testicular torsion	Rotation of testicle around spermatic cord and vascular pedicle. Commonly presents in males 12–18 years old. Characterized by acute, severe pain, high-riding testis, and absent cremasteric reflex. Treatment: surgical correction (orchiopexy) within 6 hours, manual detorsion if surgical option unavailable in timeframe. If testis is not viable, orchiectomy. Orchiopexy, when performed, should be bilateral because the contralateral testis is at risk for subsequent torsion.

Varicocele 	Dilated veins in pampiniform plexus due to ↑ venous pressure; most common cause of scrotal enlargement in adult males; most often on left side because of ↑ resistance to flow from left gonadal vein drainage into left renal vein; can cause infertility because of ↑ temperature; diagnosed by standing clinical exam/Valsalva maneuver (distension on inspection and "bag of worms" on palpation; augmented by Valsalva) or ultrasound with Doppler A; does not transilluminate. Treatment: consider surgical ligation or embolization if associated with pain or infertility.
Extragonadal germ cell tumors	Arise in midline locations. In adults, most commonly in retroperitoneum, mediastinum, pineal, and suprasellar regions. In infants and young children, sacrococcygeal teratomas are most common.

Scrotal masses	Benign scrotal lesions present as testicular masses that can be transilluminated (vs solid testicular tumors).	
Congenital hydrocele 	Common cause of scrotal swelling A in infants, due to incomplete obliteration of processus vaginalis. Most spontaneously resolve by 1 year old.	Transilluminating swelling.
Acquired hydrocele	Scrotal fluid collection usually 2° to infection, trauma, tumor. If bloody → hematocele.	
Spermatocele	Cyst due to dilated epididymal duct or rete testis.	Paratesticular fluctuant nodule.

Testicular germ cell tumors	~ 95% of all testicular tumors. Most often occur in young men. Risk factors: cryptorchidism, Klinefelter syndrome. Can present as a mixed germ cell tumor. Testicular mass that does not transilluminate.
Seminoma	Malignant; painless, homogenous testicular enlargement; most common testicular tumor. Does not occur in infancy. Large cells in lobules with watery cytoplasm and "fried egg" appearance. ↑ placental ALP. Highly radiosensitive. Late metastasis, excellent prognosis. Similar to dysgerminoma in females.
Yolk sac (endodermal sinus) tumor	Yellow, mucinous. Aggressive malignancy of testes, analogous to ovarian yolk sac tumor. Schiller-Duval bodies resemble primitive glomeruli. ↑ AFP is highly characteristic. Most common testicular tumor in boys < 3 years old.
Choriocarcinoma	Malignant, ↑ hCG. Disordered syncytiotrophoblastic and cytotrophoblastic elements. Hematogenous metastases to lungs and brain. May produce gynecomastia, symptoms of hyperthyroidism (hCG is structurally similar to LH, FSH, TSH).
Teratoma	Unlike in females, mature teratoma in adult males may be malignant. Benign in children.
Embryonal carcinoma	Malignant, hemorrhagic mass with necrosis; painful; worse prognosis than seminoma. Often glandular/papillary morphology. "Pure" embryonal carcinoma is rare; most commonly mixed with other tumor types. May be associated with ↑ hCG and normal AFP levels when pure (↑ AFP when mixed).

Testicular non–germ cell tumors

5% of all testicular tumors. Mostly benign.

Leydig cell

Golden brown color; contains Reinke crystals (eosinophilic cytoplasmic inclusions). Produces androgens or estrogens → gynecomastia in men, precocious puberty in boys.

Sertoli cell

Androblastoma from sex cord stroma.

Testicular lymphoma

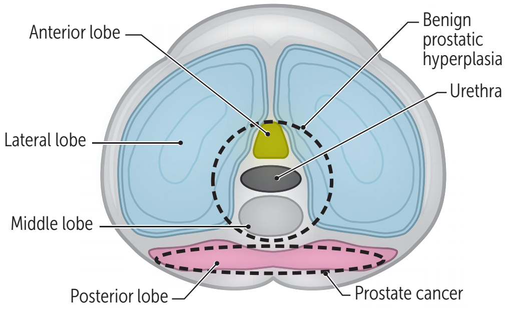
Most common testicular cancer in older men. Not a 1° cancer; arises from metastatic lymphoma to testes. Aggressive.

Benign prostatic hyperplasia

Common in men > 50 years old. Characterized by smooth, elastic, firm nodular enlargement (hyperplasia not hypertrophy) of periurethral (lateral and middle) lobes, which compress the urethra into a vertical slit. Not premalignant.

Often presents with ↑ frequency of urination, nocturia, difficulty starting and stopping urine stream, dysuria. May lead to distention and hypertrophy of bladder, hydronephrosis, UTIs. ↑ free prostate-specific antigen (PSA).

Treatment: α_1-antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle; 5α-reductase inhibitors (eg, finasteride); PDE-5 inhibitors (eg, tadalafil); surgical resection (eg, TURP, ablation).



Prostatitis

Characterized by dysuria, frequency, urgency, low back pain. Warm, tender, enlarged prostate.

Acute bacterial—in older men most common bacterium is *E coli;* in young males consider *C trachomatis*, *N gonorrhoeae.*

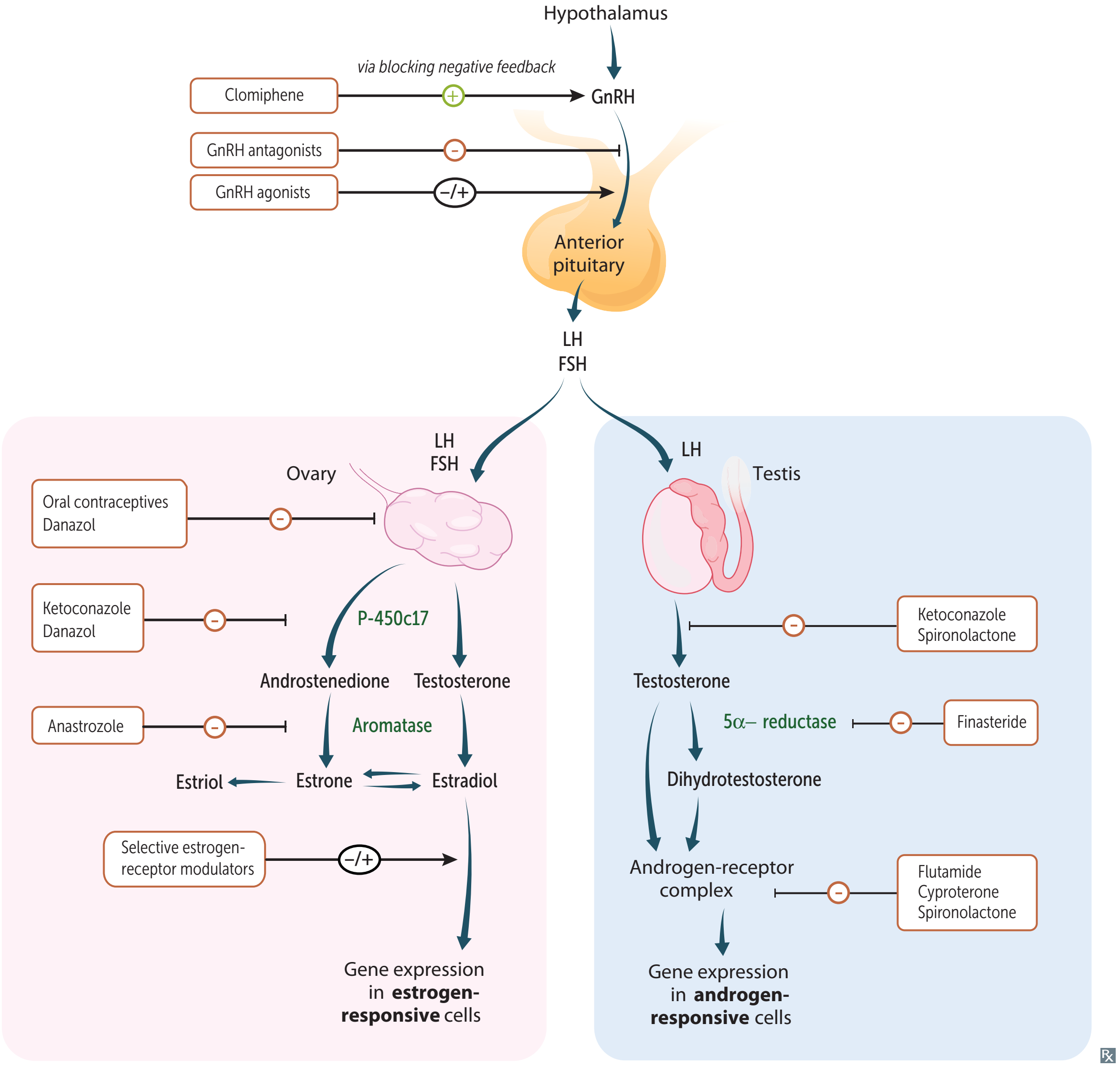
Chronic prostatitis—either bacterial or nonbacterial (eg, 2° to previous infection, nerve problems, chemical irritation).

Prostatic adenocarcinoma

Common in men > 50 years old. Arises most often from posterior lobe (peripheral zone) of prostate gland and is most frequently diagnosed by ↑ PSA and subsequent needle core biopsies. Prostatic acid phosphatase (PAP) and PSA are useful tumor markers (↑ total PSA, with ↓ fraction of free PSA). Osteoblastic metastases in bone may develop in late stages, as indicated by lower back pain and ↑ serum ALP and PSA.

▶ REPRODUCTIVE—PHARMACOLOGY

Control of reproductive hormones


Hypothalamus
via blocking negative feedback
Clomiphene
GnRH
GnRH antagonists
GnRH agonists
–/+
Anterior pituitary
LH
FSH
Ovary
LH
FSH
Oral contraceptives
Danazol
Ketoconazole
Danazol
P-450c17
Androstenedione
Testosterone
Anastrozole
Aromatase
Estriol
Estrone
Estradiol
Selective estrogen-receptor modulators
–/+
Gene expression in estrogen-responsive cells
LH
Testis
Ketoconazole
Spironolactone
Testosterone
5α– reductase
Finasteride
Dihydrotestosterone
Androgen-receptor complex
Flutamide
Cyproterone
Spironolactone
Gene expression in androgen-responsive cells

Leuprolide

MECHANISM	GnRH analog with agonist properties when used in pulsatile fashion; antagonist properties when used in continuous fashion (downregulates GnRH receptor in pituitary → ↓ FSH/LH).	**Leu**prolide can be used in **lieu** of GnRH.
CLINICAL USE	Uterine fibroids, endometriosis, precocious puberty, prostate cancer, infertility.	

Estrogens

Estrogens	Ethinyl estradiol, DES, mestranol.
MECHANISM	Bind estrogen receptors.
CLINICAL USE	Hypogonadism or ovarian failure, menstrual abnormalities, hormone replacement therapy in postmenopausal women; use in men with androgen-dependent prostate cancer.
ADVERSE EFFECTS	↑ risk of endometrial cancer (when given without progesterone), bleeding in postmenopausal women, clear cell adenocarcinoma of vagina in females exposed to DES in utero, ↑ risk of thrombi. Contraindications—ER ⊕ breast cancer, history of DVTs.

Selective estrogen receptor modulators

Clomiphene	Antagonist at estrogen receptors in hypothalamus. Prevents normal feedback inhibition and ↑ release of LH and FSH from pituitary, which stimulates ovulation. Used to treat infertility due to anovulation (eg, PCOS). May cause hot flashes, ovarian enlargement, multiple simultaneous pregnancies, visual disturbances.
Tamoxifen	Antagonist at breast; agonist at bone, uterus; ↑ risk of thromboembolic events and endometrial cancer. Used to treat and prevent recurrence of ER/PR ⊕ breast cancer.
Raloxifene	Antagonist at breast, uterus; agonist at bone; ↑ risk of thromboembolic events but no increased risk of endometrial cancer (vs tamoxifen); used primarily to treat osteoporosis.

Aromatase inhibitors

Aromatase inhibitors	Anastrozole, letrozole, exemestane.
MECHANISM	Inhibit peripheral conversion of androgens to estrogen.
CLINICAL USE	ER ⊕ breast cancer in postmenopausal women.

Hormone replacement therapy

Used for relief or prevention of menopausal symptoms (eg, hot flashes, vaginal atrophy), osteoporosis (↑ estrogen, ↓ osteoclast activity).

Unopposed estrogen replacement therapy ↑ risk of endometrial cancer, progesterone/progestin is added. Possible increased cardiovascular risk.

Progestins	Levonorgestrel, medroxyprogesterone, etonogestrel, norethindrone, megestrol, and many others when combined with estrogen.
MECHANISM	Bind progesterone receptors, ↓ growth and ↑ vascularization of endometrium, thicken cervical mucus.
CLINICAL USE	Contraception (forms include pill, intrauterine device, implant, depot injection), endometrial cancer, abnormal uterine bleeding. Progestin challenge: presence of withdrawal bleeding excludes anatomic defects (eg, Asherman syndrome) and chronic anovulation without estrogen.

Antiprogestins	Mifepristone, ulipristal.
MECHANISM	Competitive inhibitors of progestins at progesterone receptors.
CLINICAL USE	Termination of pregnancy (mifepristone with misoprostol); emergency contraception (ulipristal).

Combined contraception	Progestins and ethinyl estradiol; forms include pill, patch, vaginal ring. Estrogen and progestins inhibit LH/FSH and thus prevent estrogen surge. No estrogen surge → no LH surge → no ovulation. Progestins cause thickening of cervical mucus, thereby limiting access of sperm to uterus. Progestins also inhibit endometrial proliferation → endometrium is less suitable to the implantation of an embryo. Contraindications: smokers > 35 years old (↑ risk of cardiovascular events), patients with ↑ risk of cardiovascular disease (including history of venous thromboembolism, coronary artery disease, stroke), migraine (especially with aura), breast cancer.

Copper intrauterine device	
MECHANISM	Produces local inflammatory reaction toxic to sperm and ova, preventing fertilization and implantation; hormone free.
CLINICAL USE	Long-acting reversible contraception. Most effective emergency contraception.
ADVERSE EFFECTS	Heavier or longer menses, dysmenorrhea. Risk of PID with insertion (contraindicated in active pelvic infection).

Terbutaline, ritodrine	β_2-agonists that relax the uterus; used to ↓ contraction frequency in women during labor.

Danazol	
MECHANISM	Synthetic androgen that acts as partial agonist at androgen receptors.
CLINICAL USE	Endometriosis, hereditary angioedema.
ADVERSE EFFECTS	Weight gain, edema, acne, hirsutism, masculinization, ↓ HDL levels, hepatotoxicity, pseudotumor cerebri.

Testosterone, methyltestosterone

MECHANISM	Agonists at androgen receptors.
CLINICAL USE	Treat hypogonadism and promote development of 2° sex characteristics; stimulate anabolism to promote recovery after burn or injury.
ADVERSE EFFECTS	Masculinization in females; ↓ intratesticular testosterone in males by inhibiting release of LH (via negative feedback) → gonadal atrophy. Premature closure of epiphyseal plates. ↑ LDL, ↓ HDL.

Antiandrogens

Finasteride	5α-reductase inhibitor (↓ conversion of testosterone to DHT). Used for BPH and male-pattern baldness.	Testosterone $\xrightarrow{5\alpha\text{-reductase}}$ DHT (more potent).
Flutamide	Nonsteroidal competitive inhibitor at androgen receptors. Used for prostate carcinoma.	
Ketoconazole	Inhibits steroid synthesis (inhibits 17,20 desmolase/17α-hydroxylase).	Used in PCOS to reduce androgenic symptoms. Both can cause gynecomastia and amenorrhea.
Spironolactone	Inhibits steroid binding, 17,20 desmolase/17α-hydroxylase.	

Tamsulosin	α_1-antagonist used to treat BPH by inhibiting smooth muscle contraction. Selective for $\alpha_{1A/D}$ receptors (found on prostate) vs vascular α_{1B} receptors.

Phosphodiesterase type 5 inhibitors

Sildenafil, vardenafil, tadalafil.

MECHANISM	Inhibit PDE-5 → ↑ cGMP → prolonged smooth muscle relaxation in response to NO → ↑ blood flow in corpus cavernosum of penis, ↓ pulmonary vascular resistance.	Sildena**fil**, vardena**fil**, and tadala**fil** **fill** the penis.
CLINICAL USE	Erectile dysfunction, pulmonary hypertension, BPH (tadalafil only).	
ADVERSE EFFECTS	Headache, flushing, dyspepsia, cyanopia (blue-tinted vision). Risk of life-threatening hypotension in patients taking nitrates.	“**H**ot and sweaty,” but then **H**eadache, **H**eartburn, **H**ypotension.

Minoxidil

MECHANISM	Direct arteriolar vasodilator.
CLINICAL USE	Androgenetic alopecia (pattern baldness), severe refractory hypertension.

NOTES

Respiratory

"There's so much pollution in the air now that if it weren't for our lungs, there'd be no place to put it all."

—Robert Orben

"Freedom is the oxygen of the soul."

—Moshe Dayan

"Whenever I feel blue, I start breathing again."

—L. Frank Baum

"Life is not the amount of breaths you take; it's the moments that take your breath away."

—Will Smith, *Hitch*

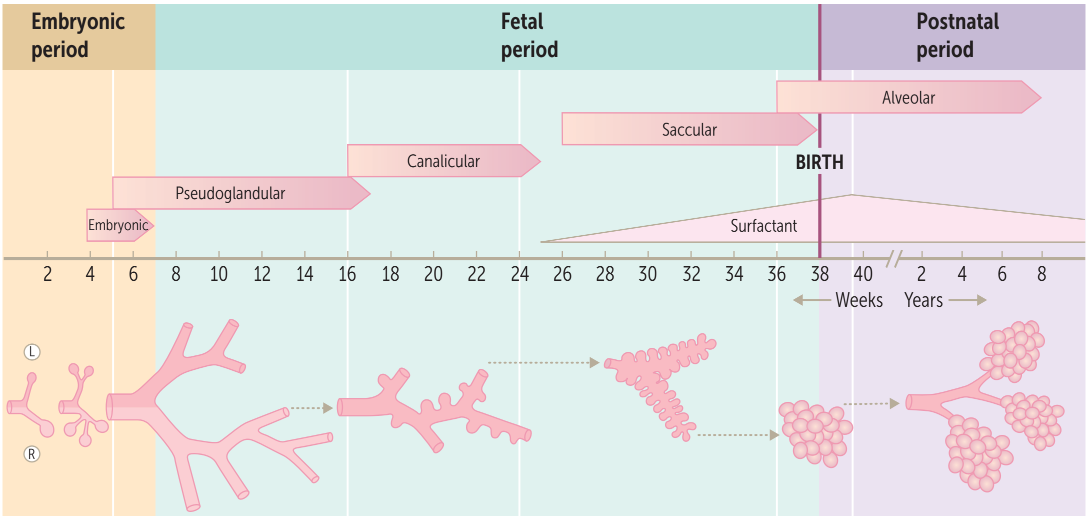
- Embryology 626
- Anatomy 628
- Physiology 630
- Pathology 636
- Pharmacology 648

▸ RESPIRATORY—EMBRYOLOGY

Lung development

Occurs in five stages. Initial development includes development of lung bud from distal end of respiratory diverticulum during week 4.

STAGE	IMPORTANT TERMS	NOTES
Embryonic (weeks 4–7)	Lung bud → trachea → bronchial buds → mainstem bronchi → secondary (lobar) bronchi → tertiary (segmental) bronchi.	Errors at this stage can lead to tracheoesophageal fistula.
Pseudoglandular (weeks 5–17)	Endodermal tubules → terminal bronchioles. Surrounded by modest capillary network.	Respiration impossible, incompatible with life.
Canalicular (weeks 16–25)	Terminal bronchioles → respiratory bronchioles → alveolar ducts. Surrounded by prominent capillary network.	Airways increase in diameter. Respiration capable at 25 weeks.
Saccular (week 26–birth)	Alveolar ducts → terminal sacs. Terminal sacs separated by 1° septae. Pneumocytes develop.	
Alveolar (week 36–8 years)	Terminal sacs → adult alveoli (due to 2° septation). In utero, "breathing" occurs via aspiration and expulsion of amniotic fluid → ↑ vascular resistance through gestation. At birth, fluid gets replaced with air → ↓ in pulmonary vascular resistance.	At birth: 20–70 million alveoli. By 8 years: 300–400 million alveoli.



Congenital lung malformations

Pulmonary hypoplasia	Poorly developed bronchial tree with abnormal histology. Associated with congenital diaphragmatic hernia (usually left-sided), bilateral renal agenesis (Potter sequence).
Bronchogenic cysts	Caused by abnormal budding of the foregut and dilation of terminal or large bronchi. Discrete, round, sharply defined, fluid-filled densities on CXR (air-filled if infected). Generally asymptomatic but can drain poorly, causing airway compression and/or recurrent respiratory infections.

Club cells

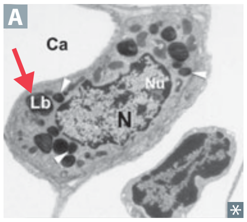
Nonciliated; low-columnar/cuboidal with secretory granules. Located in small airways. Secrete component of surfactant; degrade toxins; act as reserve cells.

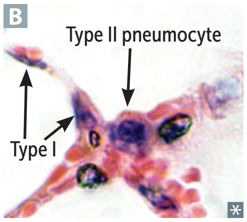
Alveolar cell types

Type I pneumocytes

97% of alveolar surfaces. Line the alveoli. Squamous; thin for optimal gas diffusion.

Type II pneumocytes





Secrete surfactant from lamellar bodies (arrow in A) → ↓ alveolar surface tension, prevents alveolar collapse, ↓ lung recoil, and ↑ compliance. Cuboidal and clustered B. Also serve as precursors to type I cells and other type II cells. Proliferate during lung damage.

Alveolar macrophages

Phagocytose foreign materials, release cytokines and alveolar proteases.

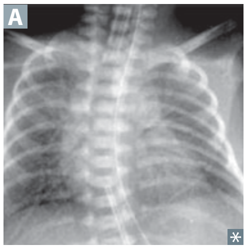
$$\text{Collapsing pressure } (P) = \frac{2\text{ (surface tension)}}{\text{radius}}$$

Alveoli have ↑ tendency to collapse on expiration as radius ↓ (law of Laplace).

Pulmonary surfactant is a complex mix of lecithins, the most important of which is dipalmitoylphosphatidylcholine (DPPC).

Surfactant synthesis begins around week 26 of gestation, but mature levels are not achieved until around week 35.

Neonatal respiratory distress syndrome



Surfactant deficiency → ↑ surface tension → alveolar collapse (“ground-glass” appearance of lung fields) A.

Risk factors: prematurity, maternal diabetes (due to ↑ fetal insulin), C-section delivery (↓ release of fetal glucocorticoids; less stressful than vaginal delivery).

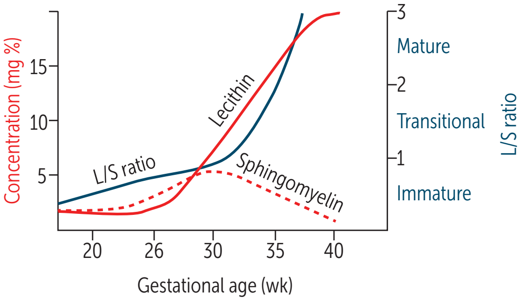
Complications: PDA, necrotizing enterocolitis.

Treatment: maternal steroids before birth; exogenous surfactant for infant.

Therapeutic supplemental O_2 can result in **R**etinopathy of prematurity, **I**ntraventricular hemorrhage, **B**ronchopulmonary dysplasia (**RIB**).

Screening tests for fetal lung maturity: lecithin-sphingomyelin (L/S) ratio in amniotic fluid (≥ 2 is healthy; < 1.5 predictive of NRDS), foam stability index test, surfactant-albumin ratio.

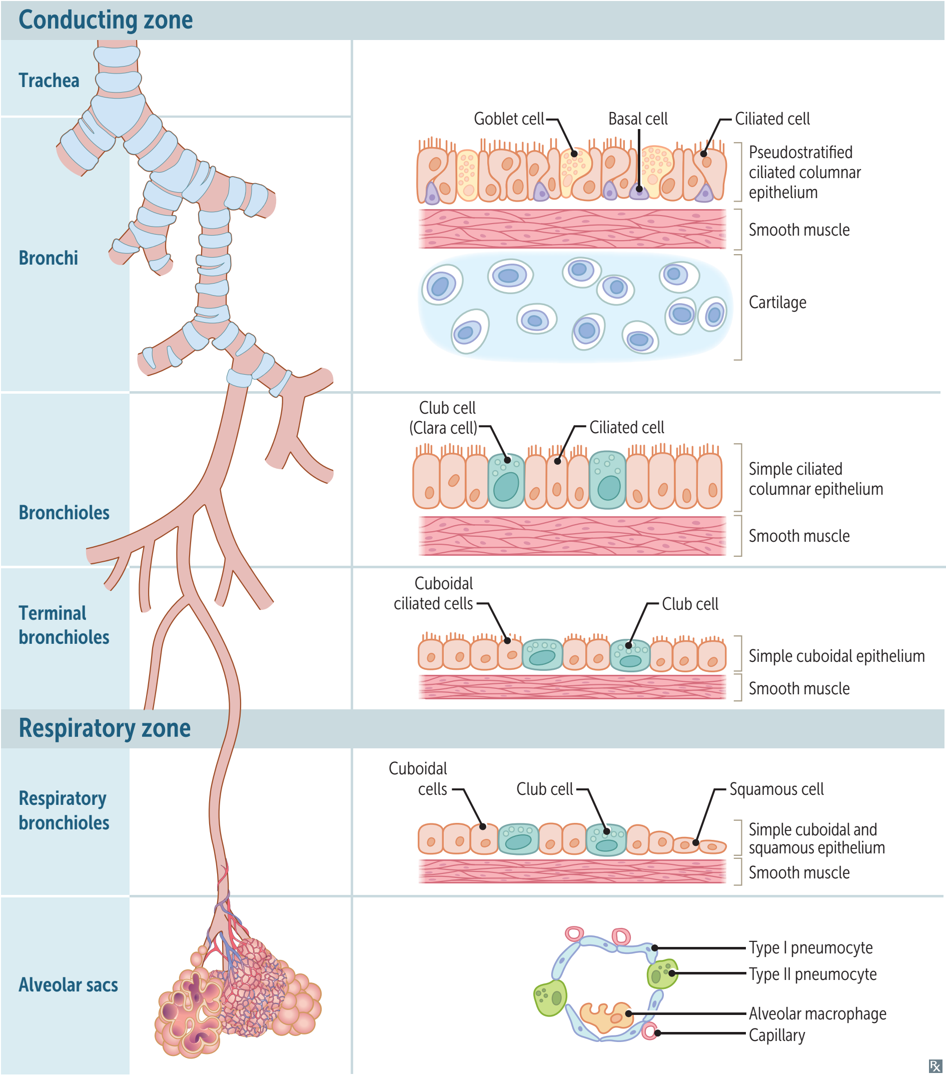
Persistently low O_2 tension → risk of PDA.



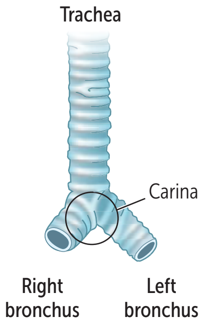
▶ RESPIRATORY—ANATOMY

Respiratory tree

Conducting zone	Large airways consist of nose, pharynx, larynx, trachea, and bronchi. Small airways consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel → least airway resistance). Warms, humidifies, and filters air but does not participate in gas exchange → "anatomic dead space." Cartilage and goblet cells extend to end of bronchi. Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus and extend to beginning of terminal bronchioles, then transition to cuboidal cells. Clear mucus and debris from lungs (mucociliary escalator). Airway smooth muscle cells extend to end of terminal bronchioles (sparse beyond this point).
Respiratory zone	Lung parenchyma; consists of respiratory bronchioles, alveolar ducts, and alveoli. Participates in gas exchange. Mostly cuboidal cells in respiratory bronchioles, then simple squamous cells up to alveoli. Cilia terminate in respiratory bronchioles. Alveolar macrophages clear debris and participate in immune response.


Conducting zone
Trachea
Bronchi
Goblet cell
Basal cell
Ciliated cell
Pseudostratified ciliated columnar epithelium
Smooth muscle
Cartilage
Bronchioles
Club cell (Clara cell)
Ciliated cell
Simple ciliated columnar epithelium
Smooth muscle
Terminal bronchioles
Cuboidal ciliated cells
Club cell
Simple cuboidal epithelium
Smooth muscle
Respiratory zone
Respiratory bronchioles
Cuboidal cells
Club cell
Squamous cell
Simple cuboidal and squamous epithelium
Smooth muscle
Alveolar sacs
Type I pneumocyte
Type II pneumocyte
Alveolar macrophage
Capillary

Lung relations

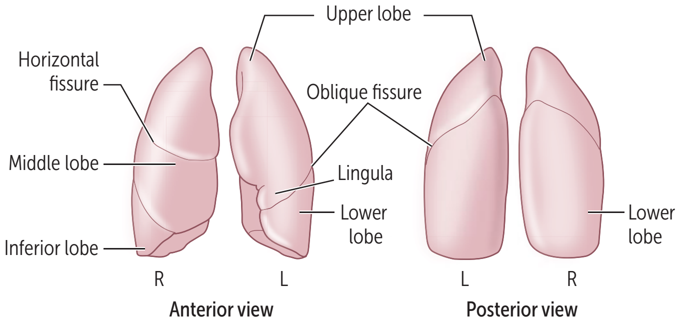

Trachea
Carina
Right bronchus
Left bronchus

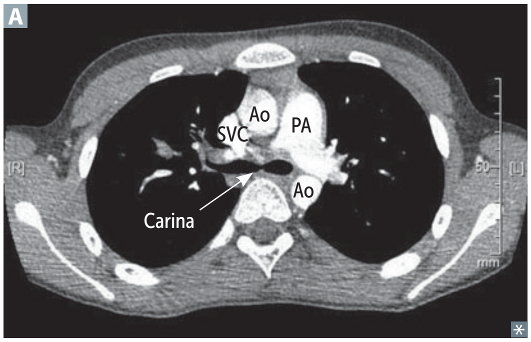
Right lung has 3 lobes; **L**eft has **L**ess **L**obes (2) and **L**ingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart.

Relation of the pulmonary artery to the bronchus at each lung hilum is described by **RALS**—**R**ight **A**nterior; **L**eft **S**uperior. Carina is posterior to ascending aorta and anteromedial to descending aorta **A**.

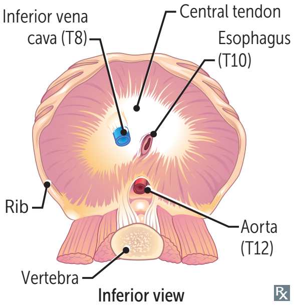
Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:

- While upright—enters basal segments of right lower lobe. Preferentially on right, but bilateral basal segments can be involved.
- While supine—enters posterior segment of right upper lobe. Preferentially on right side.


Upper lobe
Horizontal fissure
Oblique fissure
Middle lobe
Lingula
Lower lobe
Inferior lobe
Lower lobe
R
L
Anterior view
L
R
Posterior view


A
SVC
Ao
PA
Ao
Carina

Diaphragm structures


Inferior vena cava (T8)
Central tendon
Esophagus (T10)
Rib
Aorta (T12)
Vertebra
Inferior view

Structures perforating diaphragm:

- At T8: IVC, right phrenic nerve
- At T**10**: esophagus, vagus (CN **10**; 2 trunks)
- At T12: aorta (red), thoracic duct (white), azygos vein (blue) ("At **T-1-2** it's the **red**, **white**, and **blue**")

Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (eg, air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

Number of letters = T level:

T8: vena cava
T10: "oesophagus"
T12: aortic hiatus

I (IVC) **ate** (8) **ten** (10) **eggs** (esophagus) **at** (aorta) **twelve** (12).

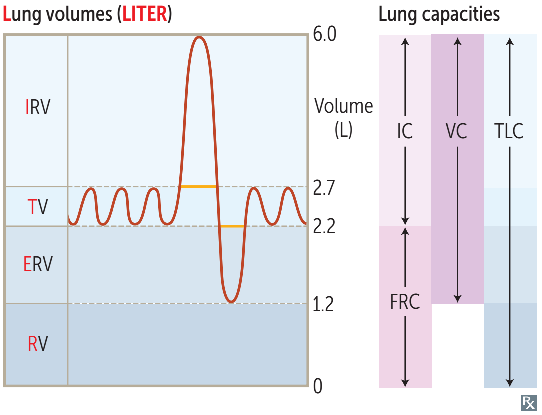
C3, 4, 5 keeps the diaphragm **alive**.

Other bifurcations:

- The common carotid bi**four**cates at C**4**.
- The trachea bi**four**cates at T**4**.
- The abdominal aorta bi**four**cates at L**4**.

▸ RESPIRATORY—PHYSIOLOGY

Lung volumes	Note: a **capacity** is a sum of ≥ 2 physiologic **volumes.**
Inspiratory reserve volume	Air that can still be breathed in after normal inspiration
Tidal volume	Air that moves into lung with each quiet inspiration, typically 500 mL
Expiratory reserve volume	Air that can still be breathed out after normal expiration
Residual volume	Air in lung after maximal expiration; RV and any lung capacity that includes RV cannot be measured by spirometry
Inspiratory capacity	IRV + TV Air that can be breathed in after normal exhalation
Functional residual capacity	RV + ERV Volume of gas in lungs after normal expiration
Vital capacity	TV + IRV + ERV Maximum volume of gas that can be expired after a maximal inspiration
Total lung capacity	IRV + TV + ERV + RV Volume of gas present in lungs after a maximal inspiration



Determination of physiologic dead space

$$V_D = V_T \times \frac{Pa_{CO_2} - Pe_{CO_2}}{Pa_{CO_2}}$$

V_D = physiologic dead space = anatomic dead space of conducting airways plus alveolar dead space; apex of healthy lung is largest contributor of alveolar dead space. Volume of inspired air that does not take part in gas exchange.

V_T = tidal volume.

Pa_{CO_2} = arterial P_{CO_2}.

Pe_{CO_2} = expired air P_{CO_2}.

Taco, Paco, Peco, Paco (refers to order of variables in equation)

Physiologic dead space—approximately equivalent to anatomic dead space in normal lungs. May be greater than anatomic dead space in lung diseases with $\dot{V}/\dot{Q}$ defects.

Pathologic dead space—when part of the respiratory zone becomes unable to perform gas exchange. Ventilated but not perfused.

Ventilation	$V_A = V_E - V_D$	
Minute ventilation (V_E)	Total volume of gas entering lungs per minute $V_E = V_T \times RR$	Normal values: Respiratory rate (RR) = 12–20 breaths/min V_T = 500 mL/breath V_D = 150 mL/breath
Alveolar ventilation (V_A)	Volume of gas per unit time that reaches alveoli $V_A = (V_T - V_D) \times RR$	

Lung and chest wall

Elastic recoil—tendency for lungs to collapse inward and chest wall to spring outward.

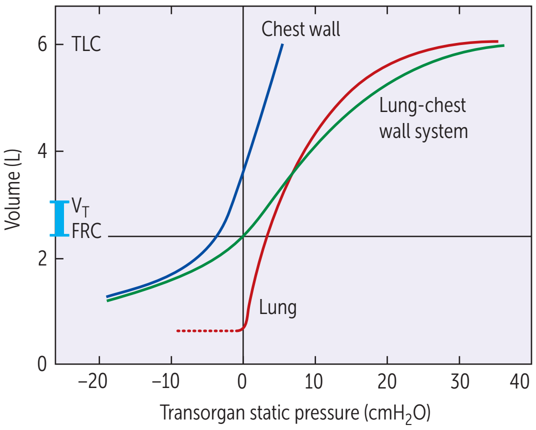
At FRC, inward pull of lung is balanced by outward pull of chest wall, and system pressure is atmospheric.

Elastic properties of both chest wall and lungs determine their combined volume.

At FRC, airway and alveolar pressures are 0, and intrapleural pressure is negative (prevents atelectasis). PVR is at minimum.

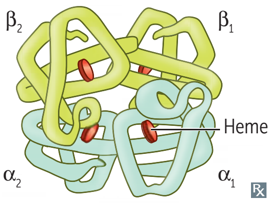
Compliance—change in lung volume for a change in pressure; expressed as $\Delta V/\Delta P$ and is inversely proportional to wall stiffness. High compliance = lung easier to fill (emphysema, normal aging), lower compliance = lung harder to fill (pulmonary fibrosis, pneumonia, NRDS, pulmonary edema). Surfactant increases compliance.

Hysteresis—lung inflation curve follows a different curve than the lung deflation curve due to need to overcome surface tension forces in inflation.



Compliant lungs **comply** (cooperate) and fill easily with air.

Hemoglobin



Hemoglobin (Hb) is composed of 4 polypeptide subunits (2 α and 2 β) and exists in 2 forms:

- Deoxygenated form has low affinity for O_2, thus promoting release/unloading of O_2.
- Oxygenated form has high affinity for O_2 (300×). Hb exhibits positive cooperativity and negative allostery.

↑ Cl^-, H^+, CO_2, 2,3-BPG, and temperature favor taut form over relaxed form (shifts dissociation curve right → ↑ O_2 unloading).

Fetal Hb (2α and 2γ subunits) has a higher affinity for O_2 than adult Hb, driving diffusion of oxygen across the placenta from mother to fetus. ↑ O_2 affinity results from ↓ affinity of HbF for 2,3-BPG.

Hemoglobin acts as buffer for H^+ ions.

Hemoglobin modifications

Lead to tissue hypoxia from ↓ O_2 saturation and ↓ O_2 content.

Methemoglobin

Oxidized form of Hb (ferric, Fe^{3+}) that does not bind O_2 as readily, but has ↑ affinity for cyanide.

Iron in Hb is normally in a reduced state (ferrous, Fe^{2+}).

Methemoglobinemia may present with cyanosis and chocolate-colored blood.

Induced methemoglobinemia (using nitrites, followed by thiosulfate) may be used to treat cyanide poisoning.

Methemoglobinemia can be treated with **meth**ylene blue and vitamin C.

Nitrites (eg, from dietary intake or polluted/high altitude water sources) and benzocaine cause poisoning by oxidizing Fe^{2+} to Fe^{3+}.

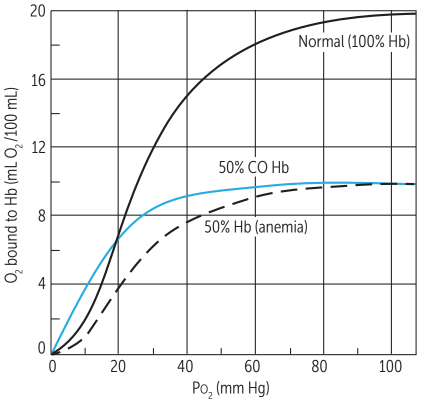
Fe^{2+} binds O_2.

Carboxyhemoglobin

Form of Hb bound to CO in place of O_2. Causes ↓ oxygen-binding capacity with left shift in oxygen-hemoglobin dissociation curve. ↓ O_2 unloading in tissues.

CO binds competitively to Hb and with 200× greater affinity than O_2.

CO poisoning can present with headaches, dizziness, and cherry red skin. May be caused by fires, car exhaust, or gas heaters. Treat with 100% O_2 and hyperbaric O_2.



Oxygen-hemoglobin dissociation curve

Sigmoidal shape due to positive cooperativity (ie, tetrameric Hb molecule can bind 4 O_2 molecules and has higher affinity for each subsequent O_2 molecule bound). Myoglobin is monomeric and thus does not show positive cooperativity; curve lacks sigmoidal appearance.

When curve shifts to the right, ↓ affinity of Hb for O_2 (facilitates unloading of O_2 to tissue).

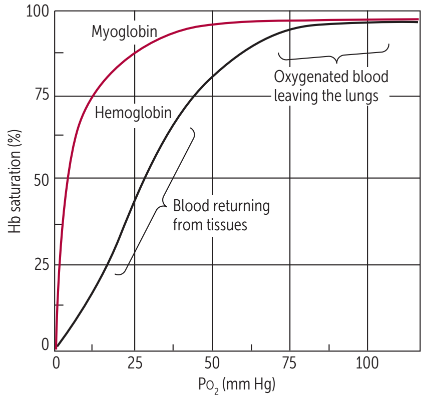
An ↑ in all factors (including H^+) causes a shift of the curve to the right.

A ↓ in all factors (including H^+) causes a left shift → ↓ O_2 unloading → renal hypoxia → ↑ EPO synthesis → compensatory erythrocytosis. **L**ower = **L**eft.

Fetal Hb has higher affinity for O_2 than adult Hb (due to low affinity for 2,3-BPG), so its dissociation curve is shifted left.

Right shift—**ACE BAT**s **right** handed:

Acid
CO_2
Exercise
2,3-**B**PG
Altitude
Temperature



Oxygen content of blood

O_2 content = $(1.34 \times \text{Hb} \times \text{Sa}O_2) + (0.003 \times \text{Pa}O_2)$
Hb = hemoglobin level
$\text{Sa}O_2$ = arterial O_2 saturation
$\text{Pa}O_2$ = partial pressure of O_2 in arterial blood

Normally 1 g Hb can bind 1.34 mL O_2; normal Hb amount in blood is 15 g/dL.
O_2 binding capacity ≈ 20.1 mL O_2/dL blood.
With ↓ Hb there is ↓ O_2 content of arterial blood, but no change in O_2 saturation and $\text{Pa}O_2$.
O_2 delivery to tissues = cardiac output × O_2 content of blood.

	Hb concentration	% O_2 sat of Hb	Dissolved O_2 ($\text{Pa}O_2$)	Total O_2 content
CO poisoning	Normal	↓ (CO competes with O_2)	Normal	↓
Anemia	↓	Normal	Normal	↓
Polycythemia	↑	Normal	Normal	↑

Pulmonary circulation

Normally a low-resistance, high-compliance system. $\text{P}O_2$ and $\text{PC}O_2$ exert opposite effects on pulmonary and systemic circulation. A ↓ in $\text{PA}O_2$ causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited—O_2 (normal health), CO_2, N_2O. Gas equilibrates early along the length of the capillary. Diffusion can be ↑ only if blood flow ↑.

Diffusion limited—O_2 (emphysema, fibrosis), CO. Gas does not equilibrate by the time blood reaches the end of the capillary.

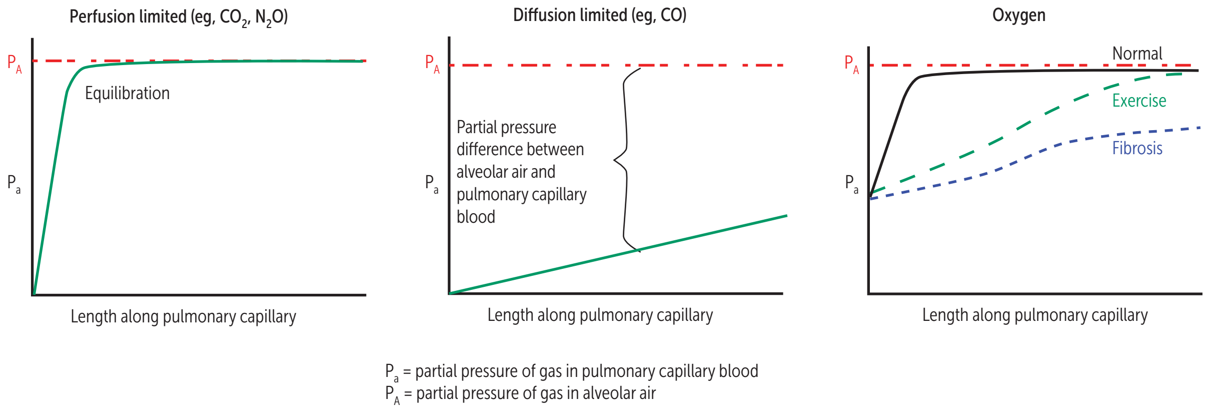
A consequence of pulmonary hypertension is cor pulmonale and subsequent right ventricular failure (jugular venous distention, edema, hepatomegaly).

Diffusion: $\dot{V}_{gas} = A \times D_k \times \frac{P_1 - P_2}{T}$ where

A = area, T = alveolar wall thickness, D_k = diffusion coefficient of gas, $P_1 - P_2$ = difference in partial pressures.

- A ↓ in emphysema.
- T ↑ in pulmonary fibrosis.

D_{LCO} is the extent to which CO, a surrogate for O_2, passes from air sacs of lungs into blood.



Pulmonary vascular resistance

$$\text{PVR} = \frac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{\text{cardiac output}}$$

R = resistance
$P_{\text{pulm artery}}$ = pressure in pulmonary artery
$P_{\text{L atrium}}$ ≈ pulmonary capillary wedge pressure

Remember: $\Delta P = Q \times R$, so $R = \Delta P / Q$
$R = 8\eta l / \pi r^4$

η = viscosity of blood; l = vessel length; r = vessel radius

Alveolar gas equation

$$P_{A}O_2 = P_{I}O_2 - \frac{P_{a}CO_2}{R}$$

$$\approx 150 \text{ mm Hg}^{a} - \frac{P_{a}CO_2}{0.8}$$

[a] At sea level breathing room air

$P_{A}O_2$ = alveolar PO_2 (mm Hg)
$P_{I}O_2$ = PO_2 in inspired air (mm Hg)
$P_{a}CO_2$ = arterial PCO_2 (mm Hg)
R = respiratory quotient = CO_2 produced/O_2 consumed
A-a gradient = $P_{A}O_2 - P_{a}O_2$. Normal range = 10–15 mm Hg
↑ A-a gradient may occur in hypoxemia; causes include shunting, $\dot{V}/\dot{Q}$ mismatch, fibrosis (impairs diffusion)

Oxygen deprivation

Hypoxia (↓ O_2 delivery to tissue)	Hypoxemia (↓ $P_{a}O_2$)	Ischemia (loss of blood flow)
↓ cardiac output	Normal A-a gradient	Impeded arterial flow
Hypoxemia	▪ High altitude	↓ venous drainage
Anemia	▪ Hypoventilation (eg, opioid use)	
CO poisoning	↑ A-a gradient	
	▪ $\dot{V}/\dot{Q}$ mismatch	
	▪ Diffusion limitation (eg, fibrosis)	
	▪ Right-to-left shunt	

Ventilation/perfusion mismatch

Ideally, ventilation is matched to perfusion (ie, $\dot{V}/\dot{Q} = 1$) for adequate gas exchange.

Lung zones:

- $\dot{V}/\dot{Q}$ at apex of lung = 3 (wasted ventilation)
- $\dot{V}/\dot{Q}$ at base of lung = 0.6 (wasted perfusion)

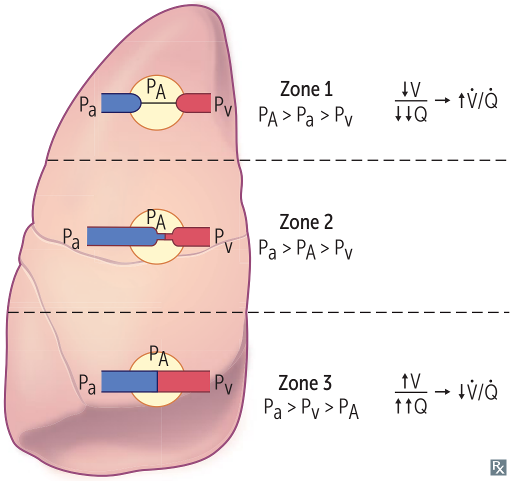
Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.

With exercise (↑ cardiac output), there is vasodilation of apical capillaries → $\dot{V}/\dot{Q}$ ratio approaches 1.

Certain organisms that thrive in high O_2 (eg, TB) flourish in the apex.

$\dot{V}/\dot{Q} = 0$ = “oirway” obstruction (shunt). In shunt, 100% O_2 does not improve $P_{a}O_2$ (eg, foreign body aspiration).

$\dot{V}/\dot{Q} = \infty$ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% O_2 improves $P_{a}O_2$ (eg, pulmonary embolus).



Carbon dioxide transport

CO_2 is transported from tissues to lungs in 3 forms:

① HCO_3^- (70%).

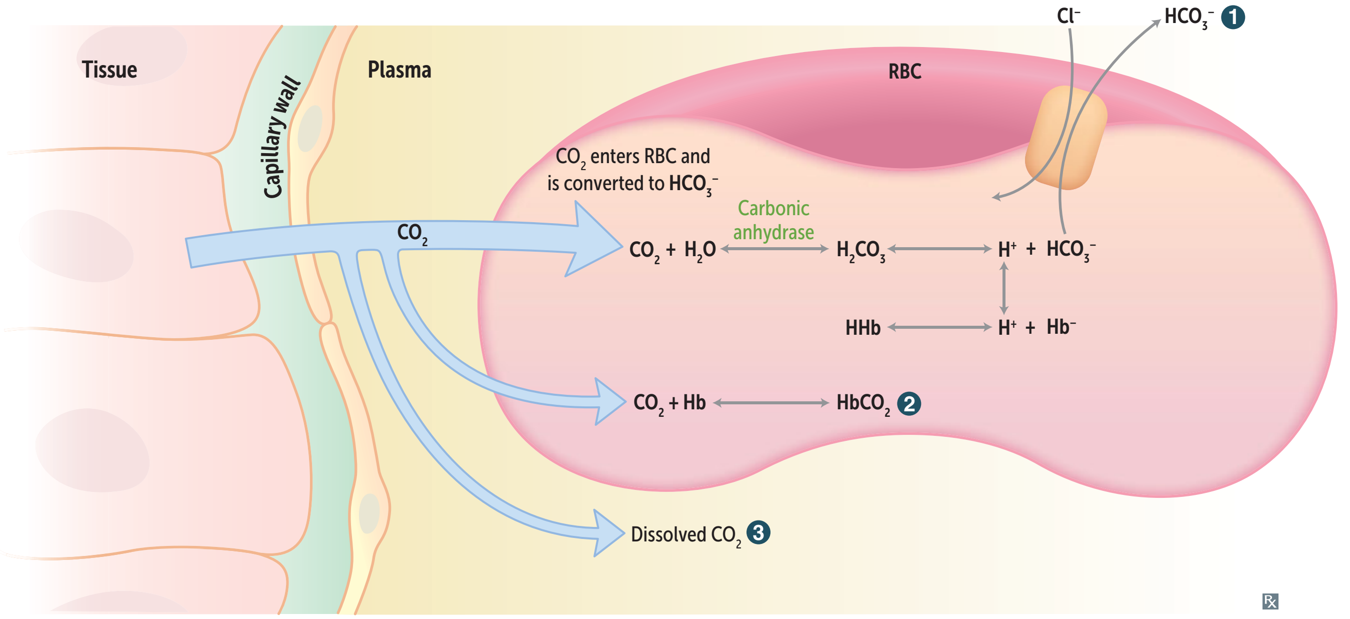
② Carbaminohemoglobin or $HbCO_2$ (21–25%). CO_2 bound to Hb at N-terminus of globin (not heme). CO_2 binding favors taut form (O_2 unloaded).

③ Dissolved CO_2 (5–9%).

In lungs, oxygenation of Hb promotes dissociation of H^+ from Hb. This shifts equilibrium toward CO_2 formation; therefore, CO_2 is released from RBCs (Haldane effect).

In peripheral tissue, ↑ H^+ from tissue metabolism shifts curve to right, unloading O_2 (Bohr effect).

Majority of blood CO_2 is carried as HCO_3^- in the plasma.


Cl⁻
HCO₃⁻ ①
Tissue
Capillary wall
Plasma
RBC
CO₂ enters RBC and is converted to HCO₃⁻
Carbonic anhydrase
CO₂
CO₂ + H₂O
H₂CO₃
H⁺ + HCO₃⁻
HHb
H⁺ + Hb⁻
CO₂ + Hb
HbCO₂ ②
Dissolved CO₂ ③

Response to high altitude

↓ atmospheric oxygen (PO_2) → ↓ Pa_{O_2} → ↑ ventilation → ↓ Pa_{CO_2} → respiratory alkalosis → altitude sickness.

Chronic ↑ in ventilation.

↑ erythropoietin → ↑ hematocrit and Hb (chronic hypoxia).

↑ 2,3-BPG (binds to Hb so that Hb releases more O_2).

Cellular changes (↑ mitochondria).

↑ renal excretion of HCO_3^- to compensate for respiratory alkalosis (can augment with acetazolamide).

Chronic hypoxic pulmonary vasoconstriction results in pulmonary hypertension and RVH.

Response to exercise

↑ CO_2 production.

↑ O_2 consumption.

↑ ventilation rate to meet O_2 demand.

$\dot{V}/\dot{Q}$ ratio from apex to base becomes more uniform.

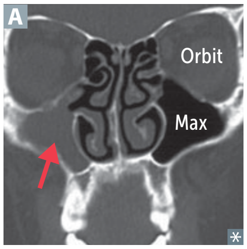
↑ pulmonary blood flow due to ↑ cardiac output.

↓ pH during strenuous exercise (2° to lactic acidosis).

No change in Pa_{O_2} and Pa_{CO_2}, but ↑ in venous CO_2 content and ↓ in venous O_2 content.

▸ RESPIRATORY—PATHOLOGY

Rhinosinusitis



Obstruction of sinus drainage into nasal cavity → inflammation and pain over affected area (typically maxillary sinuses, filled with fluid on the right in A, which drain into the middle meatus, in adults).

Most common acute cause is viral URI; may cause superimposed bacterial infection, most commonly *S pneumoniae*, *H influenzae*, *M catarrhalis*.

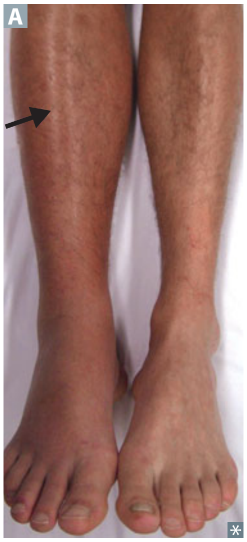
Epistaxis

Nose bleed. Most commonly occurs in anterior segment of nostril (Kiesselbach plexus). Life-threatening hemorrhages occur in posterior segment (sphenopalatine artery, a branch of maxillary artery). Common causes include foreign body, trauma, allergic rhinitis, and nasal angiofibromas.

Head and neck cancer

Mostly squamous cell carcinoma. Risk factors include tobacco, alcohol, HPV-16 (oropharyngeal), EBV (nasopharyngeal). Field cancerization: carcinogen damages wide mucosal area → multiple tumors that develop independently after exposure.

Deep venous thrombosis



Blood clot within a deep vein → swelling, redness A, warmth, pain. Predisposed by Virchow triad (SHE):

- Stasis (eg, post-op, long drive/flight)
- Hypercoagulability (eg, defect in coagulation cascade proteins, such as factor V Leiden)
- Endothelial damage (exposed collagen triggers clotting cascade)

D-dimer lab test used clinically to rule out DVT (high sensitivity, low specificity).

Most pulmonary emboli arise from proximal deep veins of lower extremity.

Use unfractionated heparin or low-molecular-weight heparins (eg, enoxaparin) for prophylaxis and acute management.

Use oral anticoagulants (eg, warfarin, rivaroxaban) for treatment (long-term prevention).

Imaging test of choice is compression ultrasound with Doppler.

Pulmonary emboli

$\dot{V}/\dot{Q}$ mismatch, hypoxemia, respiratory alkalosis. Sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia. Large emboli or saddle embolus **A** may cause sudden death.

Lines of Zahn are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish pre- and postmortem thrombi **B**.

CT pulmonary angiography is imaging test of choice for PE (look for filling defects) **C**.

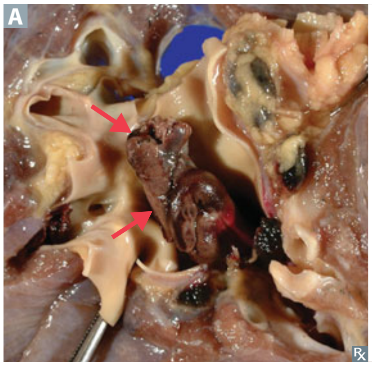
Types: **F**at, **A**ir, **T**hrombus, **B**acteria, **A**mniotic fluid, **T**umor.

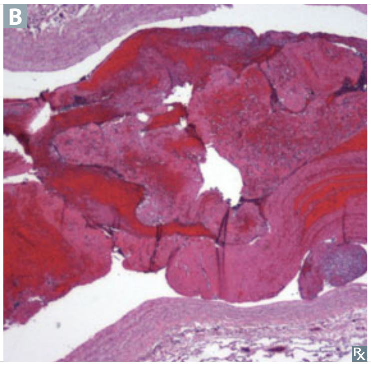
An embolus moves like a **FAT BAT**.

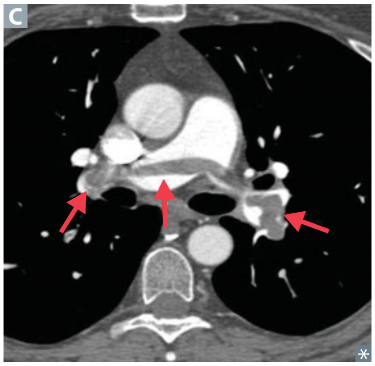
Fat emboli—associated with long bone fractures and liposuction; classic triad of hypoxemia, neurologic abnormalities, petechial rash.

Amniotic fluid emboli—can lead to DIC, especially postpartum.

Air emboli—nitrogen bubbles precipitate in ascending divers (caisson disease, decompression sickness); treat with hyperbaric O_2; or, can be iatrogenic 2° to invasive procedures (eg, central line placement).

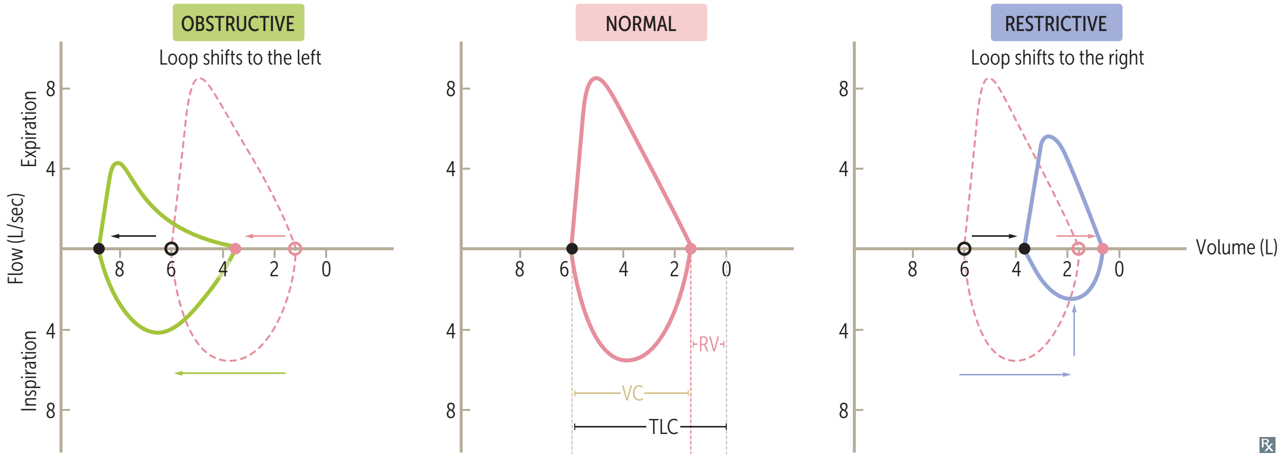






Flow volume loops

Obstructive lung volumes > normal (↑ TLC, ↑ FRC, ↑ RV); restrictive lung volumes < normal. In obstructive, FEV_1 is more dramatically reduced compared with FVC → decreased FEV_1/FVC ratio. In restrictive, FVC is more reduced or close to same compared with FEV_1 → increased or normal FEV_1/FVC ratio.



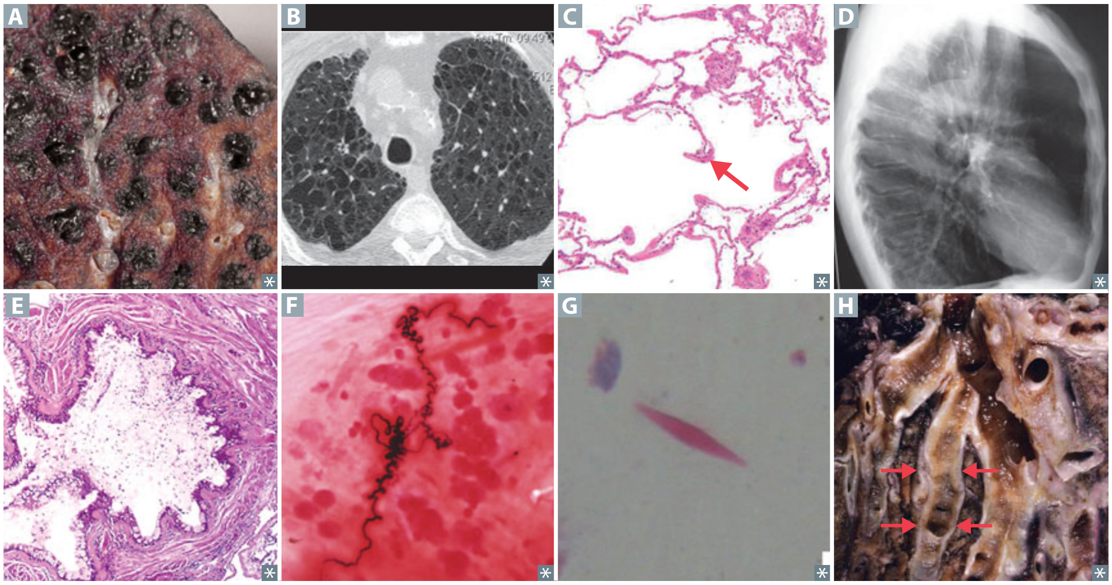
Obstructive lung diseases

Obstruction of air flow → air trapping in lungs. Airways close prematurely at high lung volumes → ↑ RV and ↑ FRC, ↑ TLC. PFTs: ↓↓ FEV_1, ↓ FVC → ↓ FEV_1/FVC ratio (hallmark), $\dot{V}/\dot{Q}$ mismatch. Chronic, hypoxic pulmonary vasoconstriction can lead to cor pulmonale. Chronic obstructive pulmonary disease (COPD) includes chronic bronchitis and emphysema.

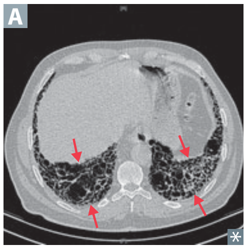
TYPE	PRESENTATION	PATHOLOGY	OTHER
Chronic bronchitis ("blue bloater")	Findings: wheezing, crackles, cyanosis (hypoxemia due to shunting), dyspnea, CO_2 retention, 2° polycythemia.	Hypertrophy and hyperplasia of mucus-secreting glands in bronchi → Reid index (thickness of mucosal gland layer to thickness of wall between epithelium and cartilage) > 50%.	Diagnostic criteria: productive cough for > 3 months in a year for > 2 consecutive years.
Emphysema ("pink puffer")	Centriacinar—associated with smoking A B. Frequently in upper lobes (smoke rises up). Panacinar—associated with α_1-antitrypsin deficiency. Frequently in lower lobes.	Enlargement of air spaces ↓ recoil, ↑ compliance, ↓ D_{LCO} from destruction of alveolar walls (arrow in C). ↑ elastase activity → ↑ loss of elastic fibers → ↑ lung compliance.	CXR: ↑ AP diameter, flattened diaphragm, ↑ lung field lucency. Barrel-shaped chest D. Exhalation through pursed lips to increase airway pressure and prevent airway collapse.
Asthma	Findings: cough, wheezing, tachypnea, dyspnea, hypoxemia, ↓ inspiratory/expiratory ratio, pulsus paradoxus, mucus plugging E. Triggers: viral URIs, allergens, stress. Diagnosis supported by spirometry and methacholine challenge.	Bronchial hyperresponsiveness → reversible bronchoconstriction. Smooth muscle hypertrophy and hyperplasia, Curschmann spirals F (shed epithelium forms whorled mucous plugs), and Charcot-Leyden crystals G (eosinophilic, hexagonal, double-pointed, needle-like crystals formed from breakdown of eosinophils in sputum).	Aspirin-induced asthma: COX inhibition → leukotriene overproduction → airway constriction. Associated with nasal polyps.

Obstructive lung diseases *(continued)*

TYPE	PRESENTATION	PATHOLOGY	OTHER
Bronchiectasis	Findings: purulent sputum, recurrent infections, hemoptysis, digital clubbing.	Chronic necrotizing infection of bronchi → permanently dilated airways.	Associated with bronchial obstruction, poor ciliary motility (eg, smoking, Kartagener syndrome), cystic fibrosis **H**, allergic bronchopulmonary aspergillosis.



Restrictive lung diseases



Restricted lung expansion causes ↓ lung volumes (↓ FVC and TLC). PFTs: FEV$_1$/FVC ratio ≥ 80%. Patient presents with short, shallow breaths.

Types:

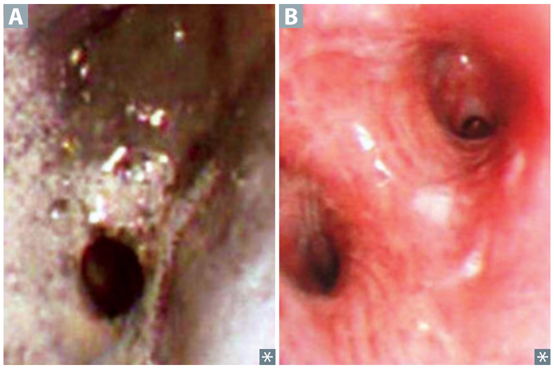
- Poor breathing mechanics (extrapulmonary, peripheral hypoventilation, normal A-a gradient):
  - Poor muscular effort—polio, myasthenia gravis, Guillain-Barré syndrome
  - Poor structural apparatus—scoliosis, morbid obesity
- Interstitial lung diseases (pulmonary ↓ diffusing capacity, ↑ A-a gradient):
  - Pneumoconioses (eg, coal workers' pneumoconiosis, silicosis, asbestosis)
  - Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granuloma; ↑ ACE and Ca^{2+}
  - Idiopathic pulmonary fibrosis **A** (repeated cycles of lung injury and wound healing with ↑ collagen deposition, "honeycomb" lung appearance and digital clubbing)
  - Granulomatosis with polyangiitis (Wegener)
  - Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
  - Hypersensitivity pneumonitis
  - Drug toxicity (bleomycin, busulfan, amiodarone, methotrexate)

Hypersensitivity pneumonitis—mixed type III/IV hypersensitivity reaction to environmental antigen. Causes dyspnea, cough, chest tightness, headache. Often seen in farmers and those exposed to birds. Reversible in early stages if stimulus is avoided.

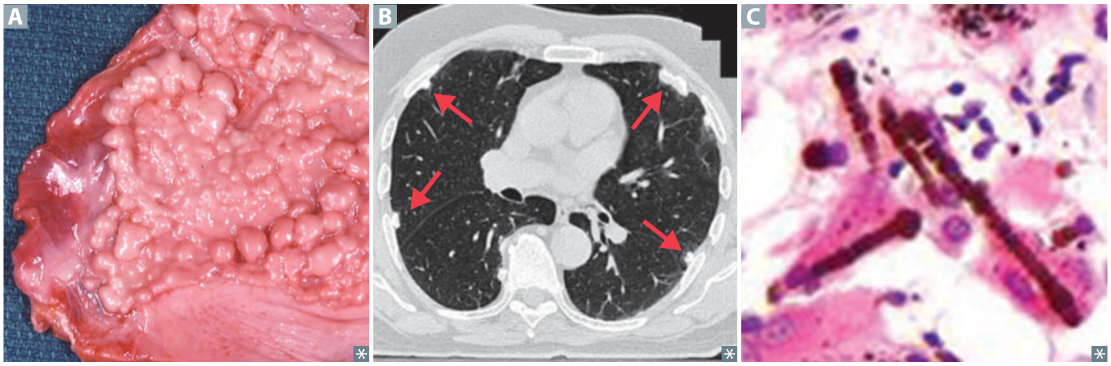
Inhalation injury and sequelae

Pulmonary complication associated with smoke and fire. Caused by heat, particulates (< 1 μm diameter), or irritants (eg, NH_3) → chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, cyanide poisoning, or arsenic poisoning.

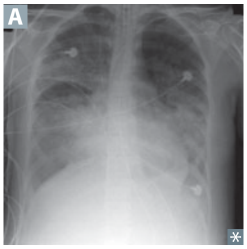
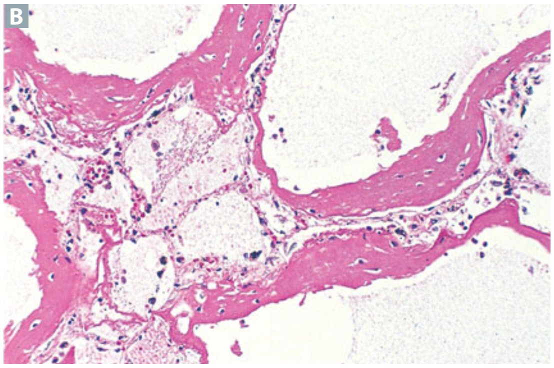
Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (A, 18 hours after inhalation injury; B, resolution at 11 days after injury).



Pneumoconioses	Coal workers' pneumoconiosis, silicosis, and asbestosis → ↑ risk of cor pulmonale, cancer, and Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).	Asbestos is from the roof (was common in insulation), but affects the base (lower lobes). Silica and coal are from the base (earth), but affect the roof (upper lobes).
Asbestosis	Associated with shipbuilding, roofing, plumbing. "Ivory white," calcified, supradiaphragmatic A and pleural B plaques are pathognomonic of asbestosis. Risk of bronchogenic carcinoma > risk of mesothelioma.	Affects lower lobes. Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells C, found in alveolar sputum sample, visualized using Prussian blue stain, often obtained by bronchoalveolar lavage. ↑ risk of pleural effusions.
Berylliosis	Associated with exposure to beryllium in aerospace and manufacturing industries. Granulomatous (noncaseating) on histology and therefore occasionally responsive to steroids.	Affects upper lobes.
Coal workers' pneumoconiosis	Prolonged coal dust exposure → macrophages laden with carbon → inflammation and fibrosis. Also known as black lung disease.	Affects upper lobes. Anthracosis—asymptomatic condition found in many urban dwellers exposed to sooty air.
Silicosis	Associated with foundries, sandblasting, mines. Macrophages respond to silica and release fibrogenic factors, leading to fibrosis. It is thought that silica may disrupt phagolysosomes and impair macrophages, increasing susceptibility to TB.	Affects upper lobes. "Eggshell" calcification of hilar lymph nodes on CXR.



Mesothelioma	Malignancy of the pleura associated with asbestosis. May result in hemorrhagic pleural effusion (exudative), pleural thickening.	Psammoma bodies seen on histology. Cytokeratin and calretinin ⊕ in almost all mesotheliomas, ⊖ in most carcinomas. Smoking not a risk factor.

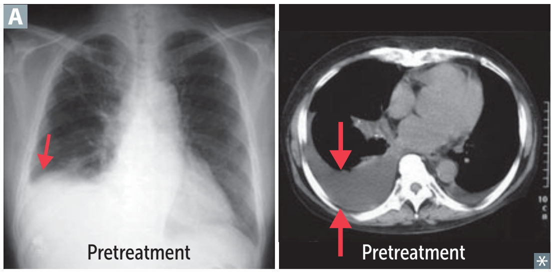
Acute respiratory distress syndrome 	Diagnosis of exclusion characterized by respiratory failure within 1 week of alveolar insult, bilateral lung opacities, ↓ $PaO_2/FiO_2 < 300$ (hypoxemia due to ↑ intrapulmonary shunting and diffusion abnormalities), no evidence of HF/fluid overload. Many causes and associations, including sepsis, pancreatitis, pneumonia, aspiration, trauma, shock. Endothelial damage → ↑ alveolar capillary permeability → protein-rich leakage into alveoli → diffuse alveolar damage and noncardiogenic pulmonary edema (normal PCWP) A. Results in formation of intra-alveolar hyaline membranes B. Initial damage due to release of neutrophilic substances toxic to alveolar wall and pulmonary capillary endothelial cells, activation of coagulation cascade, and oxygen-derived free radicals. Management: mechanical ventilation with low tidal volumes, address underlying cause. 
Sleep apnea	Repeated cessation of breathing > 10 seconds during sleep → disrupted sleep → daytime somnolence. Diagnosis confirmed by sleep study. Normal Pao_2 during the day. Nocturnal hypoxia → systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death. Hypoxia → ↑ EPO release → ↑ erythropoiesis.
Obstructive sleep apnea	Respiratory effort against airway obstruction. Associated with obesity, loud snoring. Caused by excess parapharyngeal tissue in adults, adenotonsillar hypertrophy in children. Treatment: weight loss, CPAP, surgery.
Central sleep apnea	No respiratory effort due to CNS injury/toxicity, HF, opioids. May be associated with Cheyne-Stokes respiration. Treat with positive airway pressure.
Obesity hypoventilation syndrome	Obesity ($BMI \geq 30\ kg/m^2$) → hypoventilation ↑ $PaCO_2$ during waking hours (retention); ↓ PaO_2 and ↑ $PaCO_2$ during sleep. Also known as Pickwickian syndrome.

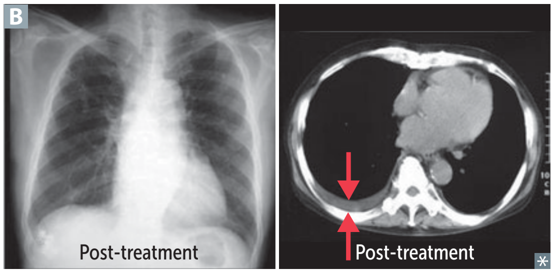
Pulmonary hypertension	Normal mean pulmonary artery pressure = 10–14 mm Hg; pulmonary hypertension ≥ 25 mm Hg at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries, plexiform lesions. Course: severe respiratory distress → cyanosis and RVH → death from decompensated cor pulmonale.
ETIOLOGIES	
Pulmonary arterial hypertension	Idiopathic PAH. Heritable PAH—often due to an inactivating mutation in *BMPR2* gene (normally inhibits vascular smooth muscle proliferation); poor prognosis. Other causes include drugs (eg, amphetamines, cocaine), connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis.
Left heart disease	Causes include systolic/diastolic dysfunction and valvular disease (eg, mitral lung).
Lung diseases or hypoxia	Destruction of lung parenchyma (eg, COPD), lung inflammation/fibrosis (eg, interstitial lung diseases), hypoxemic vasoconstriction (eg, obstructive sleep apnea, living in high altitude).
Chronic thromboembolic	Recurrent microthrombi → ↓ cross-sectional area of pulmonary vascular bed.
Multifactorial	Causes include hematologic, systemic, and metabolic disorders.

Lung—physical findings

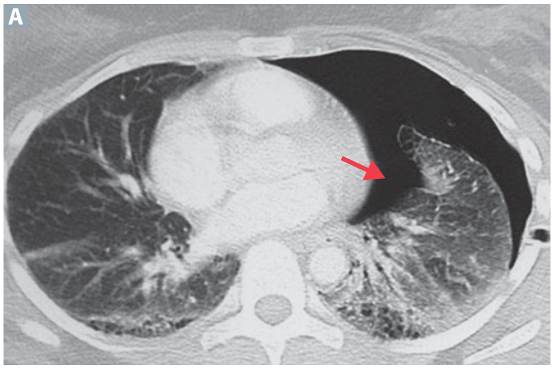
ABNORMALITY	BREATH SOUNDS	PERCUSSION	FREMITUS	TRACHEAL DEVIATION
Pleural effusion	↓	Dull	↓	— or away from side of lesion (if large)
Atelectasis (bronchial obstruction)	↓	Dull	↓	Toward side of lesion
Simple pneumothorax	↓	Hyperresonant	↓	—
Tension pneumothorax	↓	Hyperresonant	↓	Away from side of lesion
Consolidation (lobar pneumonia, pulmonary edema)	Bronchial breath sounds; late inspiratory crackles, egophony, bronchophony, whispered pectoriloquy	Dull	↑	—

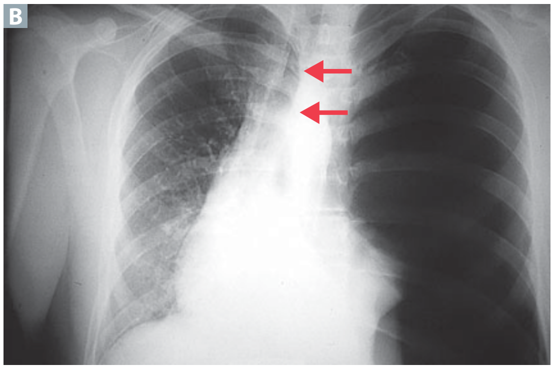
Pleural effusions	Excess accumulation of fluid A between pleural layers → restricted lung expansion during inspiration. Can be treated with thoracentesis to remove/reduce fluid B.
Transudate	↓ protein content. Due to ↑ hydrostatic pressure (eg, HF) or ↓ oncotic pressure (eg, nephrotic syndrome, cirrhosis).
Exudate	↑ protein content, cloudy. Due to malignancy, pneumonia, collagen vascular disease, trauma (occurs in states of ↑ vascular permeability). Must be drained due to risk of infection.
Lymphatic	Also known as chylothorax. Due to thoracic duct injury from trauma or malignancy. Milky-appearing fluid; ↑ triglycerides.





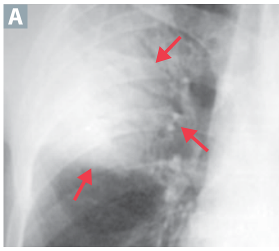
Pneumothorax	Accumulation of air in pleural space A. Dyspnea, uneven chest expansion. Chest pain, ↓ tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side.
Primary spontaneous pneumothorax	Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males.
Secondary spontaneous pneumothorax	Due to diseased lung (eg, bullae in emphysema, infections), mechanical ventilation with use of high pressures → barotrauma.
Traumatic pneumothorax	Caused by blunt (eg, rib fracture) or penetrating (eg, gunshot) trauma.
Tension pneumothorax	Can be any of the above. Air enters pleural space but cannot exit. Increasing trapped air → tension pneumothorax. Trachea deviates away from affected lung B. Needs immediate needle decompression and chest tube placement.

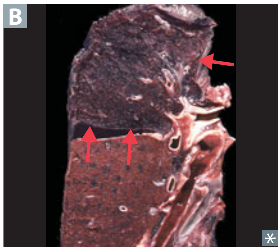


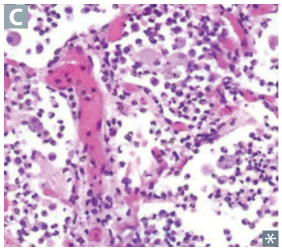


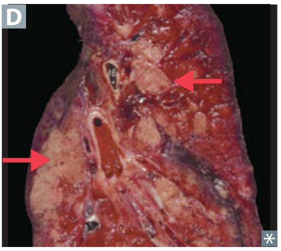
Pneumonia

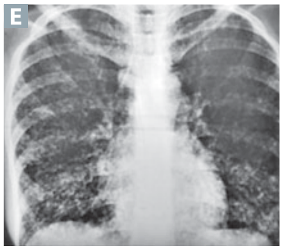
TYPE	TYPICAL ORGANISMS	CHARACTERISTICS
Lobar	*S pneumoniae* most frequently, also *Legionella*, *Klebsiella*	Intra-alveolar exudate → consolidation A; may involve entire lobe B or lung.
Bronchopneumonia	*S pneumoniae*, *S aureus*, *H influenzae*, *Klebsiella*	Acute inflammatory infiltrates C from bronchioles into adjacent alveoli; patchy distribution involving ≥ 1 lobe D.
Interstitial (atypical) pneumonia	*Mycoplasma*, *Chlamydophila pneumoniae*, *Chlamydia psittaci*, *Legionella*, viruses (RSV, CMV, influenza, adenovirus)	Diffuse patchy inflammation localized to interstitial areas at alveolar walls; diffuse distribution involving ≥ 1 lobe E. Generally follows a more indolent course (“walking” pneumonia).
Cryptogenic organizing pneumonia		Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP). Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure. Etiology unknown. Secondary organizing pneumonia caused by chronic inflammatory diseases (eg, rheumatoid arthritis) or medication side effects (eg, amiodarone). ⊖ sputum and blood cultures, no response to antibiotics.







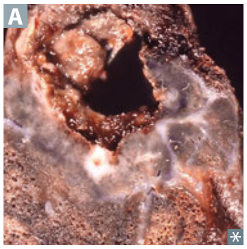


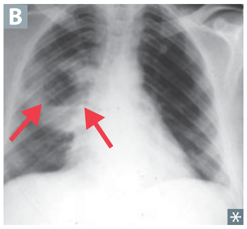


Natural history of lobar pneumonia

	Congestion	**Red hepatization**	**Gray hepatization**	**Resolution**
DAYS	1–2	3–4	5–7	8+
FINDINGS	Red-purple, partial consolidation of parenchyma Exudate with mostly bacteria	Red-brown, consolidated Exudate with fibrin, bacteria, RBCs, and WBCs	Uniformly gray Exudate full of WBCs and fibrin	Enzymes digest components of exudate

Lung abscess





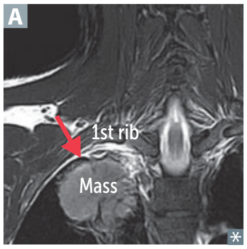
Localized collection of pus within parenchyma A. Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [eg, alcoholics, epileptics]) or bronchial obstruction (eg, cancer).

Treatment: clindamycin.

Air-fluid levels B often seen on CXR. Fluid levels common in cavities; presence suggests cavitation. Due to anaerobes (eg, *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*) or *S aureus*.

Lung abscess 2° to aspiration is most often found in right lung. Location depends on patient's position during aspiration.

Pancoast tumor (superior sulcus tumor)

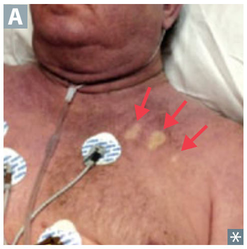


Carcinoma that occurs in the apex of lung A may cause Pancoast syndrome by invading cervical sympathetic chain.

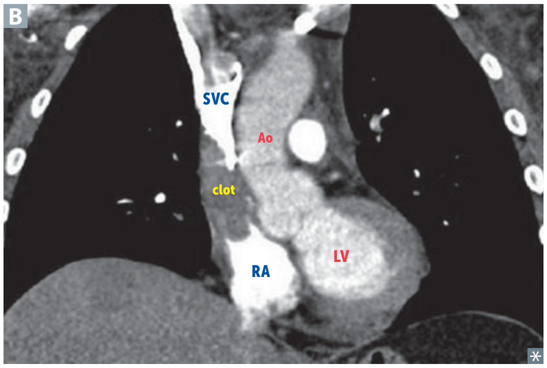
Compression of locoregional structures may cause array of findings:

- Recurrent laryngeal nerve → hoarseness
- Stellate ganglion → Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)
- Superior vena cava → SVC syndrome
- Brachiocephalic vein → brachiocephalic syndrome (unilateral symptoms)
- Brachial plexus → sensorimotor deficits

Superior vena cava syndrome

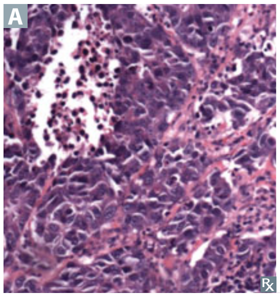


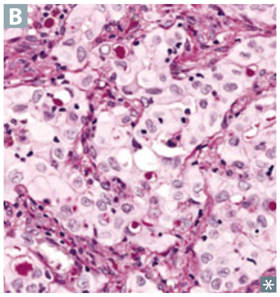
An obstruction of the SVC that impairs blood drainage from the head ("facial plethora"; note blanching after fingertip pressure in A), neck (jugular venous distention), and upper extremities (edema). Commonly caused by malignancy (eg, mediastinal mass, Pancoast tumor) and thrombosis from indwelling catheters B. Medical emergency. Can raise intracranial pressure (if obstruction is severe) → headaches, dizziness, ↑ risk of aneurysm/rupture of intracranial arteries.

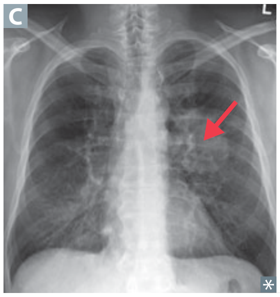


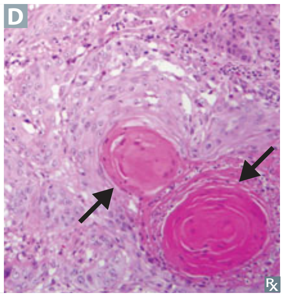
Lung cancer		
	Leading cause of cancer death. Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic "coin" lesion on CXR or noncalcified nodule on CT. Sites of metastases from lung cancer: adrenals, brain, bone (pathologic fracture), liver (jaundice, hepatomegaly). In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.	SPHERE of complications: Superior vena cava syndrome Pancoast tumor Horner syndrome Endocrine (paraneoplastic) Recurrent laryngeal nerve compression (hoarseness) Effusions (pleural or pericardial) Risk factors include smoking, secondhand smoke, radon, asbestos, family history. Squamous and Small cell carcinomas are Sentral (central) and often caused by Smoking.

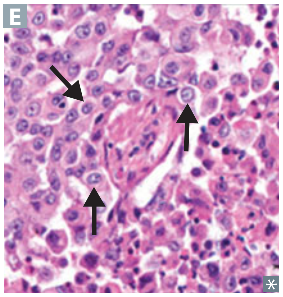
TYPE	LOCATION	CHARACTERISTICS	HISTOLOGY
Small cell			
Small cell (oat cell) carcinoma	Central	Undifferentiated → very aggressive. May produce ACTH (Cushing syndrome), SIADH, or Antibodies against presynaptic Ca^{2+} channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis, encephalitis, subacute cerebellar degeneration). Amplification of *myc* oncogenes common. Managed with chemotherapy +/– radiation.	Neoplasm of neuroendocrine Kulchitsky cells → small dark blue cells A. Chromogranin A ⊕, neuron-specific enolase ⊕.
Non–small cell			
Adenocarcinoma	Peripheral	Most common lung cancer in nonsmokers and overall (except for metastases). Activating mutations include *KRAS*, *EGFR*, and *ALK*. Associated with hypertrophic osteoarthropathy (clubbing). Bronchioloalveolar subtype (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; better prognosis. Bronchial carcinoid and bronchioloalveolar cell carcinoma have lesser association with smoking.	Glandular pattern on histology, often stains mucin ⊕ B. Bronchioloalveolar subtype: grows along alveolar septa → apparent "thickening" of alveolar walls. Tall, columnar cells containing mucus.
Squamous cell carcinoma	Central	Hilar mass C arising from bronchus; Cavitation; Cigarettes; hyperCalcemia (produces PTHrP).	Keratin pearls D and intercellular bridges.
Large cell carcinoma	Peripheral	Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically. Strong association with smoking.	Pleomorphic giant cells E.
Bronchial carcinoid tumor	—	Excellent prognosis; metastasis rare. Symptoms due to mass effect or carcinoid syndrome (flushing, diarrhea, wheezing).	Nests of neuroendocrine cells; chromogranin A ⊕.











▸ RESPIRATORY—PHARMACOLOGY

Antihistamines	Reversible inhibitors of H_1 histamine receptors.	
First generation	Diphenhydramine, dimenhydrinate, chlorpheniramine.	Names contain “-en/-ine” or “-en/-ate.”
CLINICAL USES	Allergy, motion sickness, sleep aid.	
ADVERSE EFFECTS	Sedation, antimuscarinic, anti-α-adrenergic.	
Second generation	Loratadine, fexofenadine, desloratadine, cetirizine.	Names usually end in “-adine.”
CLINICAL USES	Allergy.	
ADVERSE EFFECTS	Far less sedating than 1st generation because of ↓ entry into CNS.	

Guaifenesin	Expectorant—thins respiratory secretions; does not suppress cough reflex.

***N*-acetylcysteine**	Mucolytic—liquifies mucus in chronic bronchopulmonary diseases (eg, COPD, CF) by disrupting disulfide bonds. Also used as an antidote for acetaminophen overdose.

Dextromethorphan	Antitussive (antagonizes NMDA glutamate receptors). Synthetic codeine analog. Has mild opioid effect when used in excess. Naloxone can be given for overdose. Mild abuse potential. May cause serotonin syndrome if combined with other serotonergic agents.

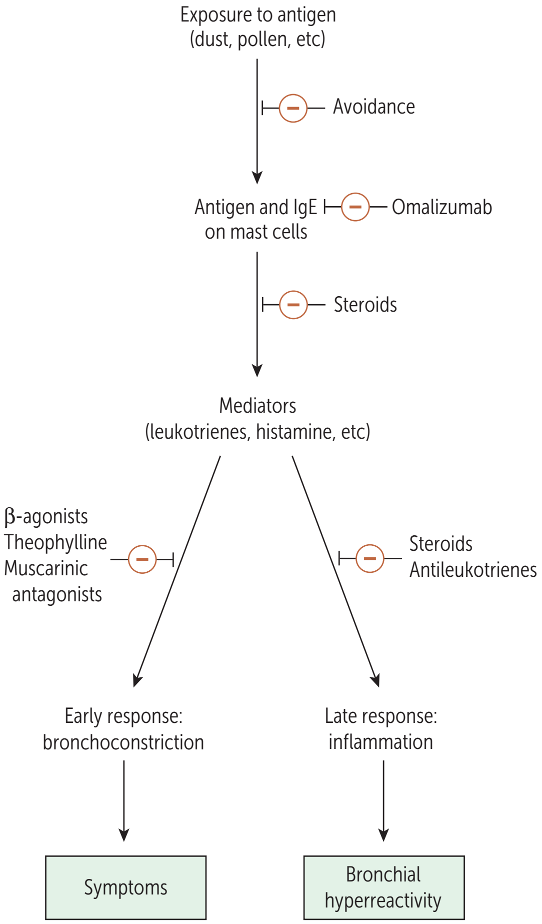
Pseudoephedrine, phenylephrine

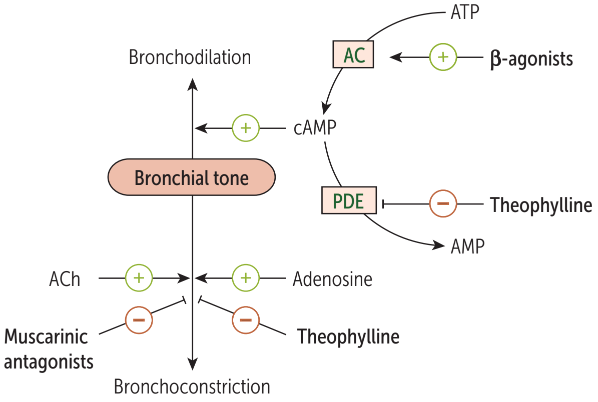
MECHANISM	α-adrenergic agonists, used as nasal decongestants.
CLINICAL USE	Reduce hyperemia, edema, nasal congestion; open obstructed eustachian tubes. Pseudoephedrine also illicitly used to make methamphetamine.
ADVERSE EFFECTS	Hypertension. Rebound congestion if used more than 4–6 days. Can also cause CNS stimulation/anxiety (pseudoephedrine).

Pulmonary hypertension drugs

DRUG	MECHANISM	CLINICAL NOTES
Bos*EN*tan	Competitively antagonizes **EN**dothelin-1 receptors → ↓ pulmonary vascular resistance.	Hepatotoxic (monitor LFTs).
Sildenafil	Inhibits PDE-5 → ↑ cGMP → prolonged vasodilatory effect of nitric oxide.	Also used to treat erectile dysfunction.
Epoprostenol, iloprost	PGI_2 (prostacyclin) with direct vasodilatory effects on pulmonary and systemic arterial vascular beds. Inhibits platelet aggregation.	Side effects: flushing, jaw pain.

Asthma drugs	Bronchoconstriction is mediated by (1) inflammatory processes and (2) parasympathetic tone; therapy is directed at these 2 pathways.
β_2-agonists	**Albuterol**—relaxes bronchial smooth muscle (short acting β_2-agonist). Used during acute exacerbation.
	Salmeterol, formoterol—long-acting agents for prophylaxis. Adverse effects are tremor and arrhythmia.
Inhaled corticosteroids	**Fluticasone, budesonide**—inhibit the synthesis of virtually all cytokines. Inactivate NF-κB, the transcription factor that induces production of TNF-α and other inflammatory agents. 1st-line therapy for chronic asthma. May cause oral thrush.
Muscarinic antagonists	**Tiotropium, ipratropium**—competitively block muscarinic receptors, preventing bronchoconstriction. Also used for COPD. Tiotropium is long acting.
Antileukotrienes	**Montelukast, zafirlukast**—block leukotriene receptors (CysLT1). Especially good for aspirin-induced and exercise-induced asthma. **Zileuton**—5-lipoxygenase pathway inhibitor. Blocks conversion of arachidonic acid to leukotrienes. Hepatotoxic.
Anti-IgE monoclonal therapy	**Omalizumab**—binds mostly unbound serum IgE and blocks binding to FcεRI. Used in allergic asthma with ↑ IgE levels resistant to inhaled steroids and long-acting β_2-agonists.
Methylxanthines	**Theophylline**—likely causes bronchodilation by inhibiting phosphodiesterase → ↑ cAMP levels due to ↓ cAMP hydrolysis. Usage is limited because of narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome P-450. Blocks actions of adenosine.


Exposure to antigen
(dust, pollen, etc)
−
Avoidance
Antigen and IgE
on mast cells
−
Omalizumab
−
Steroids
Mediators
(leukotrienes, histamine, etc)
β-agonists
Theophylline
Muscarinic
antagonists
−
−
Steroids
Antileukotrienes
Early response:
bronchoconstriction
Late response:
inflammation
Symptoms
Bronchial
hyperreactivity


ATP
AC
+
β-agonists
Bronchodilation
+
cAMP
Bronchial tone
PDE
−
Theophylline
AMP
ACh
+
+
Adenosine
−
Muscarinic
antagonists
−
Theophylline
Bronchoconstriction

Methacholine	Nonselective muscarinic receptor (M_3) agonist. Used in bronchial challenge test to help diagnose asthma.

NOTES

HIGH-YIELD SYSTEMS

Rapid Review

"Study without thought is vain: thought without study is dangerous."
—Confucius

"It is better, of course, to know useless things than to know nothing."
—Lucius Annaeus Seneca

"For every complex problem there is an answer that is clear, simple, and wrong."
—H. L. Mencken

The following tables represent a collection of high-yield associations of diseases with their clinical findings, treatments, and pathophysiology. They serve as a quick review before the exam to tune your senses to commonly tested cases.

- Classic Presentations 652
- Classic Labs/Findings 657
- Classic/Relevant Treatments 661
- Key Associations 664
- Equation Review 669

▶ CLASSIC PRESENTATIONS

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Abdominal pain, ascites, hepatomegaly	Budd-Chiari syndrome (posthepatic venous thrombosis)	375
Abdominal pain, diarrhea, leukocytosis, recent antibiotic use	*Clostridium difficile* infection	134
Achilles tendon xanthoma	Familial hypercholesterolemia (↓ LDL receptor signaling)	90
Adrenal hemorrhage, hypotension, DIC	Waterhouse-Friderichsen syndrome (meningococcemia)	138
Anaphylaxis following blood transfusion	IgA deficiency	112
Anterior "drawer sign" ⊕	Anterior cruciate ligament injury	424
Arachnodactyly, lens dislocation (upward), aortic dissection, hyperflexible joints	Marfan syndrome (fibrillin defect)	56
Athlete with polycythemia	2° to erythropoietin injection	411
Back pain, fever, night sweats	Pott disease (vertebral TB)	136
Bilateral acoustic schwannomas	Neurofibromatosis type 2	56
Bilateral hilar adenopathy, uveitis	Sarcoidosis (noncaseating granulomas)	444
Black eschar on face of patient with diabetic ketoacidosis	*Mucor* or *Rhizopus* fungal infection	149
Blue sclera	Osteogenesis imperfecta (type I collagen defect)	47
Bluish line on gingiva	Burton line (lead poisoning)	397
Bone pain, bone enlargement, arthritis	Paget disease of bone (↑ osteoblastic and osteoclastic activity)	436
Bounding pulses, wide pulse pressure, diastolic heart murmur, head bobbing	Aortic regurgitation	279
"Butterfly" facial rash and Raynaud phenomenon in a young female	Systemic lupus erythematosus	443
Café-au-lait spots, Lisch nodules (iris hamartoma), cutaneous neurofibromas, pheochromocytomas, optic gliomas	Neurofibromatosis type I	505
Café-au-lait spots (unilateral), polyostotic fibrous dysplasia, precocious puberty, multiple endocrine abnormalities	McCune-Albright syndrome (mosaic G-protein signaling mutation)	53
Calf pseudohypertrophy	Muscular dystrophy (most commonly Duchenne, due to X-linked recessive frameshift mutation of dystrophin gene)	57
Cervical lymphadenopathy, desquamating rash, coronary aneurysms, red conjunctivae and tongue, hand-foot changes	Kawasaki disease (treat with IVIG and aspirin)	302
"Cherry-red spots" on macula	Tay-Sachs (ganglioside accumulation) or Niemann-Pick (sphingomyelin accumulation), central retinal artery occlusion	84
Chest pain on exertion	Angina (stable: with moderate exertion; unstable: with minimal exertion or at rest)	293
Chest pain, pericardial effusion/friction rub, persistent fever following MI	Dressler syndrome (autoimmune-mediated post-MI fibrinous pericarditis, 2 weeks to several months after acute episode)	296

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Chest pain with ST depressions on EKG	Unstable angina (⊖ troponins) or NSTEMI (⊕ troponins)	293
Child uses arms to stand up from squat	Duchenne muscular dystrophy (Gowers sign)	57
Child with fever later develops red rash on face that spreads to body	Erythema infectiosum/fifth disease ("slapped cheeks" appearance, caused by parvovirus B19)	179
Chorea, dementia, caudate degeneration	Huntington disease (autosomal dominant CAG repeat expansion)	491
Chorioretinitis, hydrocephalus, intracranial calcifications	Congenital toxoplasmosis	152
Chronic exercise intolerance with myalgia, fatigue, painful cramps, myoglobinuria	McArdle disease (skeletal muscle glycogen phosphorylase deficiency)	83
Cold intolerance	Hypothyroidism	327
Conjugate horizontal gaze palsy, horizontal diplopia	Internuclear ophthalmoplegia (damage to MLF; may be unilateral or bilateral)	513
Continuous "machine-like" heart murmur	PDA (close with indomethacin; keep open with PGE analogs)	289
Cutaneous/dermal edema due to connective tissue deposition	Myxedema (caused by hypothyroidism, Graves disease [pretibial])	327
Cutaneous flushing, diarrhea, bronchospasm	Carcinoid syndrome (right-sided cardiac valvular lesions, ↑ 5-HIAA)	362
Dark purple skin/mouth nodules in a patient with AIDS	Kaposi sarcoma, associated with HHV-8	388
Deep, labored breathing/hyperventilation	Diabetic ketoacidosis (Kussmaul respirations)	337
Dermatitis, dementia, diarrhea	Pellagra (niacin [vitamin B_3] deficiency)	63
Dilated cardiomyopathy, edema, alcoholism or malnutrition	Wet beriberi (thiamine [vitamin B_1] deficiency)	62
Dog or cat bite resulting in infection	*Pasteurella multocida* (cellulitis at inoculation site)	144
Dry eyes, dry mouth, arthritis	Sjögren syndrome (autoimmune destruction of exocrine glands)	439
Dysphagia (esophageal webs), glossitis, iron deficiency anemia	Plummer-Vinson syndrome (may progress to esophageal squamous cell carcinoma)	396
Elastic skin, hypermobility of joints, ↑ bleeding tendency	Ehlers-Danlos syndrome (type V collagen defect, type III collagen defect seen in vascular subtype of ED)	47
Enlarged, hard left supraclavicular node	Virchow node (abdominal metastasis)	362
Episodic vertigo, tinnitus, hearing loss	Meniere disease	503
Erythroderma, lymphadenopathy, hepatosplenomegaly, atypical T cells	Mycosis fungoides (cutaneous T-cell lymphoma) or Sézary syndrome (mycosis fungoides + malignant T cells in blood)	408
Facial muscle spasm upon tapping	Chvostek sign (hypocalcemia)	331
Fat, female, forty, and fertile	Cholelithiasis (gallstones)	353
Fever, chills, headache, myalgia following antibiotic treatment for syphilis	Jarisch-Herxheimer reaction (rapid lysis of spirochetes results in endotoxin-like release)	143
Fever, cough, conjunctivitis, coryza, diffuse rash	Measles	163
Fever, night sweats, weight loss	B symptoms of lymphoma	407

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Fibrous plaques in soft tissue of penis with abnormal curvature	Peyronie disease (connective tissue disorder)	617
Golden brown rings around peripheral cornea	Wilson disease (Kayser-Fleischer rings due to copper accumulation)	378
Gout, intellectual disability, self-mutilating behavior in a boy	Lesch-Nyhan syndrome (HGPRT deficiency, X-linked recessive)	439
Hamartomatous GI polyps, hyperpigmentation of mouth/feet/hands/genitalia	Peutz-Jeghers syndrome (inherited, benign polyposis can cause bowel obstruction; ↑ cancer risk, mainly GI)	370
Hepatosplenomegaly, pancytopenia, osteoporosis, aseptic necrosis of femoral head, bone crises	Gaucher disease (glucocerebrosidase deficiency)	84
Hereditary nephritis, sensorineural hearing loss, cataracts	Alport syndrome (mutation in collagen IV)	46
Hyperphagia, hypersexuality, hyperorality, hyperdocility	Klüver-Bucy syndrome (bilateral amygdala lesion)	481
Hyperreflexia, hypertonia, Babinski sign present	UMN damage	499
Hyporeflexia, hypotonia, atrophy, fasciculations	LMN damage	499
Hypoxemia, polycythemia, hypercapnia	Chronic bronchitis (hyperplasia of mucous cells, “blue bloater”)	638
Indurated, ulcerated genital lesion	Nonpainful: chancre (1° syphilis, *Treponema pallidum*) Painful, with exudate: chancroid (*Haemophilus ducreyi*)	143 180
Infant with cleft lip/palate, microcephaly or holoprosencephaly, polydactyly, cutis aplasia	Patau syndrome (trisomy 13)	59
Infant with hypoglycemia, hepatomegaly	Cori disease (debranching enzyme deficiency) or Von Gierke disease (glucose-6-phosphatase deficiency, more severe)	83
Infant with microcephaly, rocker-bottom feet, clenched hands, and structural heart defect	Edwards syndrome (trisomy 18)	59
Jaundice, palpable distended non-tender gallbladder	Courvoisier sign (distal malignant obstruction of biliary tree)	380
Large rash with bull’s-eye appearance	Erythema chronicum migrans from *Ixodes* tick bite (Lyme disease: *Borrelia*)	142
Lucid interval after traumatic brain injury	Epidural hematoma (middle meningeal artery rupture)	483
Male child, recurrent infections, no mature B cells	Bruton disease (X-linked agammaglobulinemia)	56
Mucosal bleeding and prolonged bleeding time	Glanzmann thrombasthenia (defect in platelet aggregation due to lack of GpIIb/IIIa)	405
Muffled heart sounds, distended neck veins, hypotension	Beck triad of cardiac tamponade	300
Multiple colon polyps, osteomas/soft tissue tumors, impacted/sup\ernumerary teeth	Gardner syndrome (subtype of FAP)	370
Myopathy (infantile hypertrophic cardiomyopathy), exercise intolerance	Pompe disease (lysosomal α-1,4-glucosidase deficiency)	46
Neonate with arm paralysis following difficult birth	Erb-Duchenne palsy (superior trunk [C5–C6] brachial plexus injury: “waiter’s tip”)	428

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
No lactation postpartum, absent menstruation, cold intolerance	Sheehan syndrome (pituitary infarction)	606
Nystagmus, intention tremor, scanning speech, bilateral internuclear ophthalmoplegia	Multiple sclerosis	493
Painful blue fingers/toes, hemolytic anemia	Cold agglutinin disease (autoimmune hemolytic anemia caused by *Mycoplasma pneumoniae*, infectious mononucleosis, CLL)	401
Painful fingers/toes changing color from white to blue to red with cold or stress	Raynaud phenomenon (vasospasm in extremities)	445
Painful, raised red lesions on pads of fingers/toes	Osler nodes (infective endocarditis, immune complex deposition)	299
Painless erythematous lesions on palms and soles	Janeway lesions (infective endocarditis, septic emboli/microabscesses)	299
Painless jaundice	Cancer of the pancreatic head obstructing bile duct	380
Palpable purpura on buttocks/legs, joint pain, abdominal pain (child), hematuria	Henoch-Schönlein purpura (IgA vasculitis affecting skin and kidneys)	303
Pancreatic, pituitary, parathyroid tumors	MEN 1 (autosomal dominant)	339
Periorbital and/or peripheral edema, proteinuria (> 3.5g/day), hypoalbuminemia, hypercholesterolemia	Nephrotic syndrome	563
Pink complexion, dyspnea, hyperventilation	Emphysema ("pink puffer," centriacinar [smoking] or panacinar [α_1-antitrypsin deficiency])	638
Polyuria, renal tubular acidosis type II, growth failure, electrolyte imbalances, hypophosphatemic rickets	Fanconi syndrome (multiple combined dysfunction of the proximal convoluted tubule)	399
Pruritic, purple, polygonal planar papules and plaques (6 P's)	Lichen planus	453
Ptosis, miosis, anhidrosis	Horner syndrome (sympathetic chain lesion)	509
Pupil accommodates but doesn't react	Neurosyphilis (Argyll Robertson pupil)	143
Rapidly progressive limb weakness that ascends following GI/upper respiratory infection	Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculopathy subtype)	493
Rash on palms and soles	Coxsackie A, 2° syphilis, Rocky Mountain spotted fever	179
Recurrent cold (noninflamed) abscesses, unusual eczema, high serum IgE	Hyper-IgE syndrome (Job syndrome: neutrophil chemotaxis abnormality)	112
Red "currant jelly" sputum in alcoholic or diabetic patients	*Klebsiella pneumoniae* pneumonia	177
Red "currant jelly" stools	Acute mesenteric ischemia (adults), intussusception (children)	368 369
Red, itchy, swollen rash of nipple/areola	Paget disease of the breast (sign of underlying neoplasm)	616
Red urine in the morning, fragile RBCs	Paroxysmal nocturnal hemoglobinuria	400
Renal cell carcinoma (bilateral), hemangioblastomas, angiomatosis, pheochromocytoma	von Hippel-Lindau disease (dominant tumor suppressor gene mutation)	568
Resting tremor, rigidity, akinesia, postural instability, shuffling gait	Parkinson disease (loss of dopaminergic neurons in substantia nigra pars compacta)	490
Retinal hemorrhages with pale centers	Roth spots (bacterial endocarditis)	299

CLINICAL PRESENTATION	DIAGNOSIS/DISEASE	PAGE
Severe jaundice in neonate	Crigler-Najjar syndrome (congenital unconjugated hyperbilirubinemia)	377
Severe RLQ pain with palpation of LLQ	Rovsing sign (acute appendicitis)	366
Severe RLQ pain with deep tenderness	McBurney sign (acute appendicitis)	366
Short stature, café au lait spots, thumb/radial defects, ↑ incidence of tumors/leukemia, aplastic anemia	Fanconi anemia (genetic loss of DNA crosslink repair; often progresses to AML)	399
Single palmar crease	Down syndrome	59
Situs inversus, chronic sinusitis, bronchiectasis, infertility	Kartagener syndrome (dynein arm defect affecting cilia)	45
Skin hyperpigmentation, hypotension, fatigue	1° adrenocortical insufficiency (eg, Addison disease) causes ↑ ACTH and ↑ α-MSH production)	324
Slow, progressive muscle weakness in boys	Becker muscular dystrophy (X-linked missense mutation in dystrophin; less severe than Duchenne)	57 57
Small, irregular red spots on buccal/lingual mucosa with blue-white centers	Koplik spots (measles [rubeola] virus)	166
Smooth, moist, painless, wart-like white lesions on genitals	Condylomata lata (2° syphilis)	143
Splinter hemorrhages in fingernails	Bacterial endocarditis	299
"Strawberry tongue"	Scarlet fever Kawasaki disease	132 302
Streak ovaries, congenital heart disease, horseshoe kidney, cystic hygroma at birth, short stature, webbed neck, lymphedema	Turner syndrome (45,XO)	603
Sudden swollen/painful big toe joint, tophi	Gout/podagra (hyperuricemia)	440
Swollen gums, mucosal bleeding, poor wound healing, petechiae	Scurvy (vitamin C deficiency: can't hydroxylate proline/lysine for collagen synthesis)	65
Swollen, hard, painful finger joints	Osteoarthritis (osteophytes on PIP [Bouchard nodes], DIP [Heberden nodes])	439
Systolic ejection murmur (crescendo-decrescendo)	Aortic stenosis	279
Telangiectasias, recurrent epistaxis, skin discoloration, arteriovenous malformations, GI bleeding, hematuria	Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)	56
Thyroid and parathyroid tumors, pheochromocytoma	MEN 2A (autosomal dominant *RET* mutation)	326
Thyroid tumors, pheochromocytoma, ganglioneuromatosis	MEN 2B (autosomal dominant *RET* mutation)	339
Toe extension/fanning upon plantar scrape	Babinski sign (UMN lesion)	480
Unilateral facial drooping involving forehead	LMN facial nerve (CN VII) palsy; UMN lesions spare the forehead	502
Urethritis, conjunctivitis, arthritis in a male	Reactive arthritis associated with HLA-B27	146
Vascular birthmark (port-wine stain) of the face	Nevus flammeus (benign, but associated with Sturge-Weber syndrome)	505
Vomiting blood following gastroesophageal lacerations	Mallory-Weiss syndrome (alcoholic and bulimic patients)	360
Weight loss, diarrhea, arthritis, fever, adenopathy	Whipple disease (*Tropheryma whipplei*)	122
"Worst headache of my life"	Subarachnoid hemorrhage	483

▸ CLASSIC LABS/FINDINGS

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
↑ AFP in amniotic fluid/maternal serum	Dating error, anencephaly, spina bifida (open neural tube defects)	461
Anticentromere antibodies	Scleroderma (CREST)	446
Anti-desmoglein (anti-desmosome) antibodies	Pemphigus vulgaris (blistering)	452
Anti–glomerular basement membrane antibodies	Goodpasture syndrome (glomerulonephritis and hemoptysis)	564
Antihistone antibodies	Drug-induced SLE (eg, hydralazine, isoniazid, phenytoin, procainamide)	443
Anti-IgG antibodies	Rheumatoid arthritis (systemic inflammation, joint pannus, boutonnière deformity)	439
Antimitochondrial antibodies (AMAs)	1° biliary cirrhosis (female, cholestasis, portal hypertension)	378
Antineutrophil cytoplasmic antibodies (ANCAs)	Microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (MPO-ANCA/p-ANCA); granulomatosis with polyangiitis (Wegener; PR3-ANCA/c-ANCA); primary sclerosing cholangitis (MPO-ANCA/p-ANCA)	302 378
Antinuclear antibodies (ANAs: anti-Smith and anti-dsDNA)	SLE (type III hypersensitivity)	443
Antiplatelet antibodies	Idiopathic thrombocytopenic purpura	405
Anti-topoisomerase antibodies	Diffuse systemic scleroderma	446
Anti-transglutaminase/anti-gliadin/anti-endomysial antibodies	Celiac disease (diarrhea, weight loss)	364
"Apple core" lesion on barium enema x-ray	Colorectal cancer (usually left-sided)	371
Atypical lymphocytes	EBV	161
Azurophilic peroxidase ⊕ granular inclusions in granulocytes and myeloblasts	Auer rods (AML, especially the promyelocytic [M3] type)	410
Bacitracin response	Sensitive: *S pyogenes* (group A); resistant: *S agalactiae* (group B)	132 133
"Bamboo spine" on x-ray	Ankylosing spondylitis (chronic inflammatory arthritis: HLA-B27)	442
Basophilic nuclear remnants in RBCs	Howell-Jolly bodies (due to splenectomy or nonfunctional spleen)	395
Basophilic stippling of RBCs	Lead poisoning or sideroblastic anemia	394
Bloody or yellow tap on lumbar puncture	Subarachnoid hemorrhage	483
"Boot-shaped" heart on x-ray	Tetralogy of Fallot (due to RVH)	288
Branching gram ⊕ rods with sulfur granules	*Actinomyces israelii*	125
Bronchogenic apical lung tumor on imaging	Pancoast tumor (can compress cervical sympathetic chain and cause Horner syndrome)	264 646
"Brown" tumor of bone	Hyperparathyroidism or osteitis fibrosa cystica (deposited hemosiderin from hemorrhage gives brown color)	434

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
Cardiomegaly with apical atrophy	Chagas disease (*Trypanosoma cruzi*)	154
Cellular crescents in Bowman capsule	Rapidly progressive crescentic glomerulonephritis	564
"Chocolate cyst" of ovary	Endometriosis (frequently involves both ovaries)	610
Circular grouping of dark tumor cells surrounding pale neurofibrils	Homer-Wright rosettes (neuroblastoma, medulloblastoma)	498
Colonies of mucoid *Pseudomonas* in lungs	Cystic fibrosis (autosomal recessive mutation in *CFTR* gene → fat-soluble vitamin deficiency and mucous plugs)	56
↓ AFP in amniotic fluid/maternal serum	Down syndrome or other chromosomal abnormalities	598
Degeneration of dorsal column fibers	Tabes dorsalis (3° syphilis), subacute combined degeneration (dorsal columns, lateral corticospinal, spinocerebellar tracts affected)	143
"Delta wave" on EKG, short PR interval, supraventricular tachycardia	Wolff-Parkinson-White syndrome (Bundle of Kent bypasses AV node)	283
Depigmentation of neurons in substantia nigra	Parkinson disease (basal ganglia disorder: rigidity, resting tremor, bradykinesia)	490
Desquamated epithelium casts in sputum	Curschmann spirals (bronchial asthma; can result in whorled mucous plugs)	638
Disarrayed granulosa cells arranged around collections of eosinophilic fluid	Call-Exner bodies (granulosa cell tumor of the ovary)	611
Dysplastic squamous cervical cells with "raisinoid" nuclei and hyperchromasia	Koilocytes (HPV: predisposes to cervical cancer)	609
Electrical alternans (alternating amplitude on EKG)	Pericardial tamponade	300
Enlarged cells with intranuclear inclusion bodies	"Owl eye" appearance of CMV	161
Enlarged thyroid cells with ground-glass nuclei with central clearing	"Orphan Annie" eyes nuclei (papillary carcinoma of the thyroid)	330
Eosinophilic cytoplasmic inclusion in liver cell	Mallory body (alcoholic liver disease)	374
Eosinophilic cytoplasmic inclusion in neuron	Lewy body (Parkinson disease and Lewy body dementia)	490
Eosinophilic globule in liver	Councilman body (viral hepatitis, yellow fever), represents hepatocyte undergoing apoptosis	168
Eosinophilic inclusion bodies in cytoplasm of hippocampal and cerebellar neurons	Negri bodies of rabies	167
Extracellular amyloid deposition in gray matter of brain	Senile plaques (Alzheimer disease)	490
Giant B cells with bilobed nuclei with prominent inclusions ("owl's eye")	Reed-Sternberg cells (Hodgkin lymphoma)	407
Glomerulus-like structure surrounding vessel in germ cells	Schiller-Duval bodies (yolk sac tumor)	618
"Hair on end" ("Crew-cut") appearance on x-ray	β-thalassemia, sickle cell disease (marrow expansion)	397
hCG elevated	Choriocarcinoma, hydatidiform mole (occurs with and without embryo, and multiple pregnancy)	598
Heart nodules (granulomatous)	Aschoff bodies (rheumatic fever)	129
Heterophile antibodies	Infectious mononucleosis (EBV)	161
Hexagonal, double-pointed, needle-like crystals in bronchial secretions	Bronchial asthma (Charcot-Leyden crystals: eosinophilic granules)	638

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
High level of D-dimers	DVT, PE, DIC	392
Hilar lymphadenopathy, peripheral granulomatous lesion in middle or lower lung lobes (can calcify)	Ghon complex (1° TB: *Mycobacterium* bacilli)	136
"Honeycomb lung" on x-ray or CT	Interstitial pulmonary fibrosis	639
Hypercoagulability (leading to migrating DVTs and vasculitis)	Trousseau syndrome (adenocarcinoma of pancreas or lung)	380
Hypersegmented neutrophils	Megaloblastic anemia (B_{12} deficiency: neurologic symptoms; folate deficiency: no neurologic symptoms)	398
Hypertension, hypokalemia, metabolic alkalosis	1° hyperaldosteronism (Conn syndrome)	323
Hypochromic, microcytic anemia	Iron deficiency anemia, lead poisoning, thalassemia (fetal hemoglobin sometimes present)	396
Intranuclear eosinophilic droplet-like bodies	Cowdry type A bodies (HSV or VZV)	162
Iron-containing nodules in alveolar septum	Ferruginous bodies (asbestosis: ↑ chance of lung cancer)	641
Keratin pearls on a skin biopsy	Squamous cell carcinoma	454
Large granules in phagocytes, immunodeficiency	Chédiak-Higashi disease (congenital failure of phagolysosome formation)	113
"Lead pipe" appearance of colon on abdominal imaging	Ulcerative colitis (loss of haustra)	365
Linear appearance of IgG deposition on glomerular and alveolar basement membranes	Goodpasture syndrome	564
Low serum ceruloplasmin	Wilson disease (hepatolenticular degeneration)	378
"Lumpy bumpy" appearance of glomeruli on immunofluorescence	Poststreptococcal glomerulonephritis (due to deposition of IgG, IgM, and C3)	564
Lytic ("punched-out") bone lesions on x-ray	Multiple myeloma	409
Mammary gland ("blue domed") cyst	Fibrocystic change of the breast	615
Monoclonal antibody spike	▪ Multiple myeloma (usually IgG or IgA) ▪ Monoclonal gammopathy of undetermined significance (MGUS consequence of aging) ▪ Waldenström (M protein = IgM) macroglobulinemia ▪ Primary amyloidosis	409
Mucin-filled cell with peripheral nucleus	"Signet ring" (gastric carcinoma)	362
Narrowing of bowel lumen on barium x-ray	"String sign" (Crohn disease)	365
Necrotizing vasculitis (lungs) and necrotizing glomerulonephritis	Granulomatosis with polyangiitis (Wegener; PR3-ANCA/c-ANCA) and Goodpasture syndrome (anti–basement membrane antibodies)	564
Needle-shaped, ⊖ birefringent crystals	Gout (monosodium urate crystals)	440
Nodular hyaline deposits in glomeruli	Kimmelstiel-Wilson nodules (diabetic nephropathy)	566
Novobiocin response	Sensitive: *S epidermidis*; resistant: *S saprophyticus*	131
"Nutmeg" appearance of liver	Chronic passive congestion of liver due to right heart failure or Budd-Chiari syndrome	375
"Onion skin" periosteal reaction	Ewing sarcoma (malignant small blue cell tumor)	438
Optochin sensitivity	Sensitive: *S pneumoniae*; resistant: viridans streptococci (*S mutans*, *S sanguis*)	130
Podocyte fusion or "effacement" on electron microscopy	Minimal change disease (child with nephrotic syndrome)	566

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
Protein aggregates in neurons from hyperphosphorylation of tau protein	Neurofibrillary tangles (Alzheimer disease) and Pick bodies (Pick disease)	490
Psammoma bodies	Meningiomas, papillary thyroid carcinoma, mesothelioma, papillary serous carcinoma of the endometrium and ovary	220
Pseudopalisading tumor cells on brain biopsy	Glioblastoma multiforme	496
Raised periosteum (creating a "Codman triangle")	Aggressive bone lesion (eg, osteosarcoma, Ewing sarcoma, osteomyelitis)	438
RBC casts in urine	Glomerulonephritis	562
Rectangular, crystal-like, cytoplasmic inclusions in Leydig cells	Reinke crystals (Leydig cell tumor)	619
Recurrent infections, eczema, thrombocytopenia	Wiskott-Aldrich syndrome	113
Renal epithelial casts in urine	Intrinsic renal failure (eg, ischemia or toxic injury)	571
Rhomboid crystals, ⊕ birefringent	Pseudogout (calcium pyrophosphate dihydrate crystals)	439
Rib notching (inferior surface, on x-ray)	Coarctation of the aorta	289
Ring-enhancing brain lesion on CT/MRI in AIDS	*Toxoplasma gondii*, CNS lymphoma	152
Sheets of medium-sized lymphoid cells with scattered pale, tingible body–laden macrophages ("starry sky" histology)	Burkitt lymphoma (t[8:14] c-*myc* activation, associated with EBV; "starry sky" made up of malignant cells)	408
Silver-staining spherical aggregation of tau proteins in neurons	Pick bodies (Pick disease: progressive dementia, changes in personality)	490
"Soap bubble" in femur or tibia on x-ray	Giant cell tumor of bone (generally benign)	438
"Spikes" on basement membrane, "dome-like" subepithelial deposits	Membranous nephropathy (nephrotic syndrome)	566
Stacks of RBCs	Rouleaux formation (high ESR, multiple myeloma)	409
"Steeple" sign on frontal CXR	Croup (parainfluenza virus)	166
Bacteria-covered vaginal epithelial cells	"Clue cells" (*Gardnerella vaginalis*)	144
Streptococcus bovis bacteremia	Colon cancer	133
"Tennis racket"-shaped cytoplasmic organelles (EM) in Langerhans cells	Birbeck granules (Langerhans cell histiocytosis)	411
Thousands of polyps on colonoscopy	Familial adenomatous polyposis (autosomal dominant, mutation of APC gene)	370
Thrombi made of white/red layers	Lines of Zahn (arterial thrombus, layers of platelets/RBCs)	637
"Thumb sign" on lateral neck x-ray	Epiglottitis (*Haemophilus influenzae*)	138
Thyroid-like appearance of kidney	Chronic pyelonephritis (usually due to recurrent infections)	570
"Tram-track" appearance of capillary loops of glomerular basement membranes on light microscopy	Membranoproliferative glomerulonephritis	564
Triglyceride accumulation in liver cell vacuoles	Fatty liver disease (alcoholic or metabolic syndrome)	374
↑ uric acid levels	Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, loop and thiazide diuretics	439 440

LAB/DIAGNOSTIC FINDING	DIAGNOSIS/DISEASE	PAGE
"Waxy" casts with very low urine flow	Chronic end-stage renal disease	562
WBC casts in urine	Acute pyelonephritis	562
WBCs that look "smudged"	CLL (almost always B cell)	410
"Wire loop" glomerular capillary appearance on light microscopy	Diffuse proliferative glomerulonephritis (usually seen with lupus)	564
Yellowish CSF	Xanthochromia (eg, due to subarachnoid hemorrhage)	483

▶ CLASSIC/RELEVANT TREATMENTS

CONDITION	COMMON TREATMENT(S)	PAGE
Absence seizures	Ethosuximide	514
Acute gout attack	NSAIDs, colchicine, glucocorticoids	457
Acute promyelocytic leukemia (M3)	All-*trans* retinoic acid	410
ADHD	Methylphenidate, amphetamines, CBT, atomoxetine, guanfacine, clonidine	527 542
Alcoholism	Disulfiram, acamprosate, naltrexone, supportive care	541
Alcohol withdrawal	Long-acting benzodiazepines	528
Anorexia	Nutrition, psychotherapy, mirtazapine	537
Arrhythmia in damaged cardiac tissue	Class IB antiarrhythmic (lidocaine, mexiletine)	308
Benign prostatic hyperplasia	α_1-antagonists, 5α-reductase inhibitors, PDE-5 inhibitors	619
Bipolar disorder	Mood stabilizers (eg, lithium, valproic acid, carbamazepine), atypical antipsychotics	531
Breast cancer in postmenopausal woman	Aromatase inhibitor (anastrozole)	621
Buerger disease	Smoking cessation	302
Bulimia nervosa	SSRIs	537
Candida albicans	Topical azoles (vaginitis); nystatin, fluconazole, caspofungin (oral/esophageal); fluconazole, caspofungin, amphotericin B (systemic)	149
Carcinoid syndrome	Octreotide	382
Chlamydia trachomatis	Doxycycline (+ ceftriaxone for gonorrhea coinfection), erythromycin eye drops (conjunctivitis prophylaxis in infants)	146
Chronic gout	Xanthine oxidase inhibitors (eg, allopurinol, febuxostat); pegloticase; probenecid	440
Chronic hepatitis B or C	IFN-α (HBV and HCV); ribavirin, simeprevir, sofosbuvir (HCV)	200
Chronic myelogenous leukemia	Imatinib	410
Clostridium botulinum	Antitoxin	134
Clostridium difficile	Oral metronidazole; if refractory, oral vancomycin	134

CONDITION	COMMON TREATMENT(S)	PAGE
Clostridium tetani	Antitoxin	134
CMV	Ganciclovir, foscarnet, cidofovir	198
Crohn disease	Corticosteroids, infliximab, azathioprine	365
Cryptococcus neoformans	Fluconazole (in AIDS patients)	195
Cyclophosphamide-induced hemorrhagic cystitis	Mesna	418
Depression	SSRIs (first-line)	531
Diabetes insipidus	Desmopressin (central); hydrochlorothiazide, indomethacin, amiloride (nephrogenic)	334
Diabetes mellitus type 1	Dietary intervention (low carbohydrate) + insulin replacement	340
Diabetes mellitus type 2	Dietary intervention, oral hypoglycemics, and insulin (if refractory)	340
Diabetic ketoacidosis	Fluids, insulin, K^+	340
Drug of choice for anticoagulation during pregnancy	Heparin	413
Enterococci	Vancomycin, aminopenicillins/cephalosporins	184
Erectile dysfunction	Sildenafil, tadalafil, vardenafil	623
ER ⊕ breast cancer	Tamoxifen	621
Ethylene glycol/methanol intoxication	Fomepizole (alcohol dehydrogenase inhibitor)	239
Haemophilus influenzae (B)	Rifampin (prophylaxis)	138
Generalized anxiety disorder	SSRIs, SNRIs (first line); buspirone (second line)	533
Granulomatosis with polyangiitis (Wegener)	Cyclophosphamide, corticosteroids	302
Heparin reversal	Protamine sulfate	413
HER2/neu ⊕ breast cancer	Trastuzumab	421
Hyperaldosteronism	Spironolactone	576
Hypercholesterolemia	Statin (first-line)	306
Hypertriglyceridemia	Fibrate	306
Immediate anticoagulation	Heparin	413
Infertility	Leuprolide, GnRH (pulsatile), clomiphene	619 621
Influenza	Oseltamivir, zanamivir	197
Kawasaki disease	IVIG, high-dose aspirin	302
Legionella pneumophila	Macrolides (eg, azithromycin)	139
Long-term anticoagulation	Warfarin, dabigatran, rivaroxaban and apixaban	414
Malaria	Chloroquine, mefloquine, atovaquone/proguanil (for blood schizont), primaquine (for liver hypnozoite)	153
Malignant hyperthermia	Dantrolene	513
Medical abortion	Mifepristone	622
Migraine	Abortive therapies (eg, sumatriptan, NSAIDs); prophylaxis (eg, propranolol, topiramate, CCBs, amitriptyline)	504

CONDITION	COMMON TREATMENT(S)	PAGE
Multiple sclerosis	Disease-modifying therapies (eg, β-interferon, natalizumab); for acute flares, use IV steroids	493
Mycobacterium tuberculosis	RIPE (rifampin, isoniazid, pyrazinamide, ethambutol)	192
Neisseria gonorrhoeae	Ceftriaxone (add doxycycline to cover likely concurrent *C trachomatis*)	138
Neisseria meningitidis	Penicillin/ceftriaxone, rifampin (prophylaxis)	138
Neural tube defect prevention	Prenatal folic acid	582
Osteomalacia/rickets	Vitamin D supplementation	66
Osteoporosis	Calcium/vitamin D supplementation (prophylaxis); bisphosphonates, PTH analogs, SERMs, calcitonin, denosumab (treatment)	66
Patent ductus arteriosus	Close with indomethacin; keep open with PGE analogs	289
Pheochromocytoma	α-antagonists (eg, phenoxybenzamine)	326
Pneumocystis jirovecii	TMP-SMX (prophylaxis and treatment in immunosuppressed patients)	194
Prolactinoma	Cabergoline/bromocriptine (dopamine agonists)	332
Prostate adenocarcinoma/uterine fibroids	Leuprolide, GnRH (continuous)	621
Prostate adenocarcinoma	Flutamide	623
Pseudomonas aeruginosa	Antipseudomonal penicillins, aminoglycosides, carbapenems	139
Pulmonary arterial hypertension (idiopathic)	Sildenafil, bosentan, epoprostenol	648
Rickettsia rickettsii	Doxycycline, chloramphenicol	145
Schizophrenia (negative symptoms)	Atypical antipsychotics	543
Schizophrenia (positive symptoms)	Typical and atypical antipsychotics	543
SIADH	Fluid restriction, IV hypertonic saline, conivaptan/tolvaptan, demeclocycline	334
Sickle cell disease	Hydroxyurea (↑ fetal hemoglobin)	400
Sporothrix schenckii	Itraconazole, oral potassium iodide	150
Stable angina	Sublingual nitroglycerin	305
Staphylococcus aureus	MSSA: nafcillin, oxacillin, dicloxacillin (antistaphylococcal penicillins); MRSA: vancomycin, daptomycin, linezolid, ceftaroline	184
Streptococcus bovis	Penicillin prophylaxis; evaluation for colon cancer if linked to endocarditis	133
Streptococcus pneumoniae	Penicillin/cephalosporin (systemic infection, pneumonia), vancomycin (meningitis)	132
Streptococcus pyogenes	Penicillin prophylaxis	194
Temporal arteritis	High-dose steroids	302
Tonic-clonic seizures	Levetiracetam, phenytoin, valproate, carbamazepine	510
Toxoplasma gondii	Sulfadiazine + pyrimethamine	152

CONDITION	COMMON TREATMENT(S)	PAGE
Treponema pallidum	Penicillin	182
Trichomonas vaginalis	Metronidazole (patient and partner)	177
Trigeminal neuralgia (tic douloureux)	Carbamazepine	514
Ulcerative colitis	5-ASA preparations (eg, mesalamine), 6-mercaptopurine, infliximab, colectomy	365
UTI prophylaxis	TMP-SMX	190
Warfarin reversal	Fresh frozen plasma (acute), vitamin K (non-acute)	414

▸ KEY ASSOCIATIONS

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Actinic (solar) keratosis	Precursor to squamous cell carcinoma	454
Acute gastric ulcer associated with CNS injury	Cushing ulcer (↑ intracranial pressure stimulates vagal gastric H^+ secretion)	362
Acute gastric ulcer associated with severe burns	Curling ulcer (greatly reduced plasma volume results in sloughing of gastric mucosa)	362
Age ranges for patient with ALL/CLL/AML/CML	ALL: child, CLL: adult > 60, AML: adult ~ 65, CML: adult 45–85	410
Alternating areas of transmural inflammation and normal colon	Skip lesions (Crohn disease)	365
Aortic aneurysm, abdominal	Atherosclerosis	292
Aortic aneurysm, ascending or arch	3° syphilis (syphilitic aortitis), vasa vasorum destruction	292
Aortic aneurysm, thoracic	Marfan syndrome (idiopathic cystic medial degeneration)	292
Aortic dissection	Hypertension	293
Atrophy of the mammillary bodies	Wernicke encephalopathy (thiamine deficiency causing ataxia, ophthalmoplegia, and confusion)	481
Autosplenectomy (fibrosis and shrinkage)	Sickle cell disease (hemoglobin S)	400
Bacteria associated with gastritis, peptic ulcer disease, and gastric malignancies (eg, adenocarcinoma, MALToma)	*H pylori*	142
Bacterial meningitis (adults and elderly)	*S pneumoniae*	176
Bacterial meningitis (newborns and kids)	Group B streptococcus/*E coli*/*Listeria monocytogenes* (newborns), *S pneumoniae*/*N meningitidis* (kids/teens)	176
Bilateral ovarian metastases from gastric carcinoma	Krukenberg tumor (mucin-secreting signet ring cells)	362
Bleeding disorder with GpIb deficiency	Bernard-Soulier syndrome (defect in platelet adhesion to von Willebrand factor)	405
Brain tumor (adults)	Supratentorial: metastasis, astrocytoma (including glioblastoma multiforme), meningioma, schwannoma	496
Brain tumor (kids)	Infratentorial: medulloblastoma (cerebellum) or supratentorial: craniopharyngioma	498
Breast cancer	Invasive ductal carcinoma	616

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Breast mass	Fibrocystic change, carcinoma (in postmenopausal women)	613
Breast tumor (benign, young woman)	Fibroadenoma	615
Cardiac 1° tumor (kids)	Rhabdomyoma, often seen in tuberous sclerosis	301
Cardiac manifestation of lupus	Marantic/thrombotic endocarditis (nonbacterial)	299
Cardiac tumor (adults)	Metastasis, myxoma (90% in left atrium; "ball valve")	301
Cerebellar tonsillar herniation	Chiari I malformation	462
Chronic arrhythmia	Atrial fibrillation (associated with high risk of emboli)	284
Chronic atrophic gastritis (autoimmune)	Predisposition to gastric carcinoma (can also cause pernicious anemia)	362
Clear cell adenocarcinoma of the vagina	DES exposure in utero	609
Congenital adrenal hyperplasia, hypotension	21-hydroxylase deficiency	318
Congenital cardiac anomaly	VSD	290
Congenital conjugated hyperbilirubinemia (black liver)	Dubin-Johnson syndrome (inability of hepatocytes to secrete conjugated bilirubin into bile)	377
Constrictive pericarditis	TB (developing world); idiopathic, viral illness (developed world)	300
Cretinism	Iodine deficit/congenital hypothyroidism	328
Cushing syndrome	▪ Iatrogenic (from corticosteroid therapy) ▪ Adrenocortical adenoma (secretes excess cortisol) ▪ ACTH-secreting pituitary adenoma (Cushing disease) ▪ Paraneoplastic (due to ACTH secretion by tumors)	323
Cyanosis (early; less common)	Tetralogy of Fallot, transposition of great vessels, truncus arteriosus	288
Death in CML	Blast crisis	410
Death in SLE	Lupus nephropathy	443
Dementia	Alzheimer disease, multiple infarcts (vascular dementia)	490
Demyelinating disease in young women	Multiple sclerosis	493
DIC	Severe sepsis, obstetric complications, cancer, burns, trauma, major surgery, acute pancreatitis, APL	406
Diverticulum in pharynx	Zenker diverticulum (diagnosed by barium swallow)	367
Ejection click	Aortic stenosis	279
Esophageal cancer	Squamous cell carcinoma (worldwide); adenocarcinoma (US)	361
Food poisoning (exotoxin mediated)	*S aureus*, *B cereus*	174
Gastric cancer	Adenocarcinoma	362
Glomerulonephritis (adults)	Berger disease (IgA nephropathy)	564
Gynecologic malignancy	Endometrial carcinoma (most common in US); cervical carcinoma (most common worldwide)	608
Heart murmur, congenital	Mitral valve prolapse	279
Heart valve in bacterial endocarditis	Mitral > aortic (rheumatic fever), tricuspid (IV drug abuse)	299

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Helminth infection (US)	*Ascaris lumbricoides*	155
Hematoma—epidural	Rupture of middle meningeal artery (trauma; lentiform shaped)	479
Hematoma—subdural	Rupture of bridging veins (crescent shaped)	479
Hemochromatosis	Multiple blood transfusions or hereditary *HFE* mutation (can result in heart failure, "bronze diabetes," and ↑ risk of hepatocellular carcinoma)	378
Hepatocellular carcinoma	Cirrhotic liver (associated with hepatitis B and C and with alcoholism)	372
Hereditary bleeding disorder	von Willebrand disease	406
Hereditary harmless jaundice	Gilbert syndrome (benign congenital unconjugated hyperbilirubinemia)	377
HLA-B27	Psoriatic arthritis, ankylosing spondylitis, IBD-associated arthritis, reactive arthritis (formerly Reiter syndrome)	442
HLA-DR3	Diabetes mellitus type 1, SLE, Graves disease, Hashimoto thyroiditis (also associated with HLA-DR5), Addison disease	337
HLA-DR4	Diabetes mellitus type 1, rheumatoid arthritis, Addison disease	337
Holosystolic murmur	VSD, tricuspid regurgitation, mitral regurgitation	279
Hypercoagulability, endothelial damage, blood stasis	Virchow triad (↑ risk of thrombosis)	636
Hypertension, 2°	Renal artery stenosis, chronic kidney disease (eg, polycystic kidney disease, diabetic nephropathy), hyperaldosteronism	290
Hypoparathyroidism	Accidental excision during thyroidectomy	330
Hypopituitarism	Pituitary adenoma (usually benign tumor)	335
Infection 2° to blood transfusion	Hepatitis C	168
Infections in chronic granulomatous disease	*S aureus*, *E coli*, *Aspergillus* (catalase ⊕)	113
Intellectual disability	Down syndrome, fragile X syndrome	59
Kidney stones	▪ Calcium = radiopaque ▪ Struvite (ammonium) = radiopaque (formed by urease ⊕ organisms such as *Klebsiella*, *Proteus* species, and *S saprophyticus*) ▪ Uric acid = radiolucent ▪ Cystine = radiolucent	567
Late cyanotic shunt (uncorrected left to right becomes right to left)	Eisenmenger syndrome (caused by ASD, VSD, PDA; results in pulmonary hypertension/polycythemia)	289
Liver disease	Alcoholic cirrhosis	374
Lysosomal storage disease	Gaucher disease	84
Malignancy associated with noninfectious fever	Hodgkin lymphoma	407
Malignancy (kids)	Leukemia, brain tumors	410 498
Metastases to bone	Prostate, breast > lung, thyroid, kidney	221

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Metastases to brain	Lung > breast > prostate > melanoma > GI	221
Metastases to liver	Colon >> stomach > pancreas	221
Microcytic anemia	Iron deficiency	396
Mitochondrial inheritance	Disease occurs in both males and females, inherited through females only	55
Mitral valve stenosis	Rheumatic heart disease	279
Mixed (UMN and LMN) motor neuron disease	Amyotrophic lateral sclerosis	500
Myocarditis	Coxsackie B	145
Nephrotic syndrome (adults)	Membranous nephropathy	566
Nephrotic syndrome (kids)	Minimal change disease	566
Neuron migration failure	Kallmann syndrome (hypogonadotropic hypogonadism and anosmia)	604
Nosocomial pneumonia	*S aureus*, *Pseudomonas*, other enteric gram ⊖ rods	181
Obstruction of male urinary tract	BPH	568
Opening snap	Mitral stenosis	279
Opportunistic infection in AIDS	*Pneumocystis jirovecii* pneumonia	150
Osteomyelitis	*S aureus* (most common overall)	131
Osteomyelitis in sickle cell disease	*Salmonella*	176
Osteomyelitis with IV drug use	*Pseudomonas*, *Candida*, *S aureus*	176
Ovarian tumor (benign, bilateral)	Serous cystadenoma	610
Ovarian tumor (malignant)	Serous cystadenocarcinoma	611
Pancreatitis (acute)	Gallstones, alcohol	380
Pancreatitis (chronic)	Alcohol (adults), cystic fibrosis (kids)	380
Pelvic inflammatory disease	*C trachomatis*, *N gonorrhoeae*	138
Philadelphia chromosome t(9;22) (*BCR-ABL*)	CML (may sometimes be associated with ALL/AML)	410
Pituitary tumor	Prolactinoma, somatotropic adenoma	496
1° amenorrhea	Turner syndrome (45,XO or 45,XO/46,XX mosaic)	603
1° bone tumor (adults)	Multiple myeloma	409
1° hyperaldosteronism	Adrenal hyperplasia or adenoma	560
1° hyperparathyroidism	Adenomas, hyperplasia, carcinoma	332
1° liver cancer	Hepatocellular carcinoma (chronic hepatitis, cirrhosis, hemochromatosis, α_1-antitrypsin deficiency, Wilson disease)	372
Pulmonary hypertension	Idiopathic, heritable, left heart disease (eg, HF), lung disease (eg, COPD), hypoxemic vasoconstriction (eg, OSA), thromboembolic (eg, PE)	633
Recurrent inflammation/thrombosis of small/medium vessels in extremities	Buerger disease (strongly associated with tobacco)	302
Refractory peptic ulcers and high gastrin levels	Zollinger-Ellison syndrome (gastrinoma of duodenum or pancreas), associated with MEN1	338

DISEASE/FINDING	MOST COMMON/IMPORTANT ASSOCIATIONS	PAGE
Renal tumor	Renal cell carcinoma: associated with von Hippel-Lindau and cigarette smoking; paraneoplastic syndromes (EPO, renin, PTHrP, ACTH)	568
Right heart failure due to a pulmonary cause	Cor pulmonale	633
S3 heart sound	↑ ventricular filling pressure (eg, mitral regurgitation, HF), common in dilated ventricles	276
S4 heart sound	Stiff/hypertrophic ventricle (aortic stenosis, restrictive cardiomyopathy)	276
2° hyperparathyroidism	Hypocalcemia of chronic kidney disease	319 559
Sexually transmitted disease	*C trachomatis* (usually coinfected with *N gonorrhoeae*)	146
SIADH	Small cell carcinoma of the lung	647
Site of diverticula	Sigmoid colon	366
Sites of atherosclerosis	Abdominal aorta > coronary artery > popliteal artery > carotid artery	292
t(14;18)	Follicular lymphomas (*BCL-2* activation, anti-apoptotic oncogene)	408
t(8;14)	Burkitt lymphoma (c-*myc* fusion, transcription factor oncogene)	408
t(9;22)	Philadelphia chromosome, CML (*BCR-ABL* activation, tyrosine kinase oncogene)	418
Temporal arteritis	Risk of ipsilateral blindness due to occlusion of ophthalmic artery; polymyalgia rheumatica	211
Testicular tumor	Seminoma (malignant, radiosensitive), ↑ placental ALP	618
Thyroid cancer	Papillary carcinoma (childhood irradiation)	330
Tumor in women	Leiomyoma (estrogen dependent, not precancerous)	612
Tumor of infancy	Strawberry hemangioma (grows rapidly and regresses spontaneously by childhood)	450
Tumor of the adrenal medulla (adults)	Pheochromocytoma (usually benign)	326
Tumor of the adrenal medulla (kids)	Neuroblastoma (malignant)	325
Type of Hodgkin lymphoma	Nodular sclerosing (vs mixed cellularity, lymphocytic predominance, lymphocytic depletion)	407
Type of non-Hodgkin lymphoma	Diffuse large B-cell lymphoma	408
UTI	*E coli*, *Staphylococcus saprophyticus* (young women)	140
Vertebral compression fracture	Osteoporosis (type I: postmenopausal woman; type II: elderly man or woman)	435
Viral encephalitis affecting temporal lobe	HSV-1	481
Vitamin deficiency (USA)	Folate (pregnant women are at high risk; body stores only 3- to 4-month supply; prevents neural tube defects)	64

▶ EQUATION REVIEW

TOPIC	EQUATION	PAGE
Sensitivity	Sensitivity = TP / (TP + FN)	247
Specificity	Specificity = TN / (TN + FP)	247
Positive predictive value	PPV = TP / (TP + FP)	247
Negative predictive value	NPV = TN / (FN + TN)	247
Odds ratio (for case-control studies)	$OR = \frac{a/c}{b/d} = \frac{ad}{bc}$	248
Relative risk	$RR = \frac{a/(a+b)}{c/(c+d)}$	248
Attributable risk	$AR = \frac{a}{a+b} - \frac{c}{c+d}$	248
Relative risk reduction	RRR = 1 – RR	248
Absolute risk reduction	$ARR = \frac{c}{c+d} - \frac{a}{a+b}$	248
Number needed to treat	NNT = 1/ARR	248
Number needed to harm	NNH = 1/AR	248
Hardy-Weinberg equilibrium	$p^2 + 2pq + q^2 = 1$ $p + q = 1$	53
Volume of distribution	$V_d = \frac{\text{amount of drug in the body}}{\text{plasma drug concentration}}$	225
Half-life	$t_{1/2} = \frac{0.693 \times V_d}{CL}$	225
Drug clearance	$CL = \frac{\text{rate of elimination of drug}}{\text{plasma drug concentration}} = V_d \times K_e$ (elimination constant)	225
Loading dose	$LD = \frac{C_p \times V_d}{F}$	225
Maintenance dose	$D = \frac{C_p \times CL \times \tau}{F}$	225
Cardiac output	$CO = \frac{\text{rate of } O_2 \text{ consumption}}{\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}}$ CO = stroke volume × heart rate	272 272
Mean arterial pressure	MAP = cardiac output × total peripheral resistance MAP = ⅔ diastolic + ⅓ systolic	272 272
Stroke volume	SV = EDV – ESV	273
Ejection fraction	$EF = \frac{SV}{EDV} = \frac{EDV - ESV}{EDV}$	273

TOPIC	EQUATION	PAGE
Resistance	$\text{Resistance} = \dfrac{\text{driving pressure } (\Delta P)}{\text{flow } (Q)} = \dfrac{8\eta \text{ (viscosity)} \times \text{length}}{\pi r^4}$	274
Capillary fluid exchange	$J_v = \text{net fluid flow} = K_f[(P_c - P_i) - \varsigma(\pi_c - \pi_i)]$	287
Renal clearance	$C_x = U_x V/P_x$	552
Glomerular filtration rate	$\text{GFR} = U_{\text{inulin}} \times V/P_{\text{inulin}} = C_{\text{inulin}}$ $\text{GFR} = K_f\,[(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$	552
Effective renal plasma flow	$\text{eRPF} = U_{PAH} \times \dfrac{V}{P_{PAH}} = C_{PAH}$	552
Renal blood flow	$\text{RBF} = \dfrac{\text{RPF}}{1 - \text{Hct}}$	552
Filtration fraction	$\text{FF} = \dfrac{\text{GFR}}{\text{RPF}}$	553
Henderson-Hasselbalch equation (for extracellular pH)	$\text{pH} = 6.1 + \log \dfrac{[\text{HCO}_3^-]}{0.03\ P\text{CO}_2}$	561
Winters formula	$P\text{CO}_2 = 1.5\ [\text{HCO}_3^-] + 8 \pm 2$	561
Physiologic dead space	$V_D = V_T \times \dfrac{Pa\text{CO}_2 - PE\text{CO}_2}{Pa\text{CO}_2}$	630
Pulmonary vascular resistance	$\text{PVR} = \dfrac{P_{\text{pulm artery}} - P_{\text{L atrium}}}{\text{cardiac output}}$	634
Alveolar gas equation	$PA\text{O}_2 = PI\text{O}_2 - \dfrac{Pa\text{CO}_2}{R}$	634

SECTION IV

Top-Rated Review Resources

"Some books are to be tasted, others to be swallowed, and some few to be chewed and digested."

—Sir Francis Bacon

"Always read something that will make you look good if you die in the middle of it."

—P.J. O'Rourke

"So many books, so little time."

—Frank Zappa

"If one cannot enjoy reading a book over and over again, there is no use in reading it at all."

—Oscar Wilde

- How to Use the Database 672
- Question Banks 674
- Question Books 674
- Web and Mobile Apps 674
- Comprehensive 675
- Anatomy, Embryology, and Neuroscience 675
- Behavioral Science 676
- Biochemistry 676
- Cell Biology and Histology 677
- Microbiology and Immunology 677
- Pathology 677
- Pharmacology 678
- Physiology 679

HOW TO USE THE DATABASE

This section is a database of top-rated basic science review books, sample examination books, software, websites, and apps that have been marketed to medical students studying for the USMLE Step 1. For each recommended resource, we list (where applicable) the **Title**, the **First Author** (or editor), the **Current Publisher**, the **Copyright Year**, the **Number of Pages**, the **Approximate List Price**, the **Format** of the resource, and the **Number of Test Questions**. Finally, each recommended resource receives a **Rating**. Within each section, resources are arranged first by Rating and then alphabetically by the first author within each Rating group.

For a complete list of resources, including summaries that describe their overall style and utility, go to www.firstaidteam.com/bonus.

A letter rating scale with six different grades reflects the detailed student evaluations for **Rated Resources**. Each rated resource receives a rating as follows:

A+	Excellent for boards review.
A A–	Very good for boards review; choose among the group.
B+ B	Good, but use only after exhausting better resources.
B–	Fair, but there are many better resources in the discipline; or low-yield subject material.

The Rating is meant to reflect the overall usefulness of the resource in helping medical students prepare for the USMLE Step 1. This is based on a number of factors, including:

- The cost
- The readability of the text
- The appropriateness and accuracy of the material
- The quality and number of sample questions
- The quality of written answers to sample questions
- The quality and appropriateness of the illustrations (eg, graphs, diagrams, photographs)
- The length of the text (longer is not necessarily better)
- The quality and number of other resources available in the same discipline
- The importance of the discipline for the USMLE Step 1

Please note that ratings do not reflect the quality of the resources for purposes other than reviewing for the USMLE Step 1. Many books with lower ratings are well written and informative but are not ideal for boards preparation. We have not listed or commented on general textbooks available in the basic sciences.

Evaluations are based on the cumulative results of formal and informal surveys of thousands of medical students at many medical schools across the country. The ratings represent a consensus opinion, but there may have been a broad range of opinion or limited student feedback on any particular resource.

Please note that the data listed are subject to change in that:

- Publishers' prices change frequently.
- Bookstores often charge an additional markup.
- New editions come out frequently, and the quality of updating varies.
- The same book may be reissued through another publisher.

We actively encourage medical students and faculty to submit their opinions and ratings of these basic science review materials so that we may update our database. (See p. xvii, How to Contribute.) In addition, we ask that publishers and authors submit for evaluation review copies of basic science review books, including new editions and books not included in our database. We also solicit reviews of new books or suggestions for alternate modes of study that may be useful in preparing for the examination, such as flash cards, computer software, commercial review courses, apps, and Web sites.

Disclaimer/Conflict of Interest Statement

No material in this book, including the ratings, reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through our blog at www.firstaidteam.com. Please note that USMLE-Rx and the entire *First Aid for the USMLE* series are publications by the senior authors of this book; the following ratings are based solely on recommendations from the student authors of this book as well as data from the student survey and feedback forms.

▶ TOP-RATED REVIEW RESOURCES

Question Banks

		AUTHOR	PUBLISHER	TYPE	PRICE
A+	***UWorld Qbank***	UWorld	www.uworld.com	Test/2400 q	$129–$599
A	***USMLE-Rx Qmax***	MedIQ Learning	www.usmle-rx.com	Test/2300 q	$99–$299
A–	***Kaplan Qbank***	Kaplan	www.kaptest.com	Test/2200 q	$99–$199
B+	***USMLE Consult***	Elsevier	www.usmleconsult.com	Test/2500 q	$75–$185

Question Books

		AUTHOR	PUBLISHER	TYPE	PRICE
A–	***First Aid Q&A for the USMLE Step 1***	Le	McGraw-Hill, 2012, 784 pages	Test/1000 q	$46.00
B+	***Kaplan USMLE Step 1 Qbook***	Kaplan	Kaplan, 2015, 456 pages	Test/850 q	$49.99
B+	***PreTest Clinical Vignettes for the USMLE Step 1***	McGraw-Hill	McGraw-Hill, 2010, 318 pages	Test/322 q	$41.00

Web and Mobile Apps

		AUTHOR	PUBLISHER	TYPE	PRICE
A	***Anki***		www.ankisrs.net	Flash cards	Free/$24.99
A	***First Aid Step 1 Express***		www.usmle-rx.com	Review/Test	$99–$349
A	***SketchyMedical***		www.SketchyMedical.com	Review	$169–$249
B+	***Cram Fighter***		www.cramfighter.com	Study plan	$29–$99
B+	***Firecracker***	Firecracker Inc.	www.firecracker.me	Review/ Test/1500 q	$300–$660
B+	***First Aid Step 1 Flash Facts***		https://www.usmle-rx.com	Flash cards	$49–$149
B+	***Memorang***	Memorang Inc.	www.memorangapp.com	Flash cards	Free/$99
B+	***WebPath: The Internet Pathology Laboratory***		library.med.utah.edu/WebPath/	Review/ Test/1300 q	Free
B	***Blue Histology***		www.lab.anhb.uwa.edu.au/mb140	Review/Test	Free
B	***Dr. Najeeb Lectures***		www.drnajeeblectures.com	Review	$49–$69
B	***Medical School Pathology***		www.medicalschoolpathology.com	Review	Free
B	***Osmosis***		www.osmosis.org	Test	$31–$599
B	***Radiopaedia.org***		www.radiopaedia.org	Cases/Test	Free
B	***The Pathology Guy***	Friedlander	www.pathguy.com	Review	Free
B	***Picmonic***		www.picmonic.com	Review	$24–$399
B	***The Whole Brain Atlas***	Johnson	www.med.harvard.edu/aanlib/	Review	Free
B–	***Digital Anatomist Project: Interactive Atlases***	University of Washington	www9.biostr.washington.edu/da.html	Review	Free

Comprehensive

		AUTHOR	PUBLISHER	TYPE	PRICE
A	***First Aid for the Basic Sciences: General Principles***	Le	McGraw-Hill, 2011, 576 pages	Review	$72.00
A	***First Aid for the Basic Sciences: Organ Systems***	Le	McGraw-Hill, 2011, 880 pages	Review	$93.00
A	***medEssentials for the USMLE Step 1***	Manley	Kaplan, 2012, 588 pages	Review	$54.99
A−	***Crush Step 1: The Ultimate USMLE Step 1 Review***	O'Connell	Saunders, 2013, 680 pages	Review	$41.95
A−	***USMLE Step 1 Secrets in Color***	Brown	Elsevier, 2016, 800 pages	Review	$42.99
A−	***First Aid Cases for the USMLE Step 1***	Le	McGraw-Hill, 2012, 448 pages	Cases	$50.00
B+	***Step-Up to USMLE Step 1 2015***	Jenkins	Lippincott Williams & Wilkins, 2014, 528 pages	Review	$54.99
B+	***Cracking the USMLE Step 1***	Princeton Review	Princeton Review, 2013, 832 pages	Review	$44.99
B+	***USMLE Images for the Boards: A Comprehensive Image-Based Review***	Tully	Elsevier, 2012, 296 pages	Review	$42.95
B	***Déjà Review: USMLE Step 1***	Naheedy	McGraw-Hill, 2010, 416 pages	Review	$25.00
B−	***USMLE Step 1 Made Ridiculously Simple***	Carl	MedMaster, 2015, 416 pages	Review/Test 100 q	$29.95

Anatomy, Embryology, and Neuroscience

		AUTHOR	PUBLISHER	TYPE	PRICE
A−	***High-Yield Embryology***	Dudek	Lippincott Williams & Wilkins, 2013, 176 pages	Review	$39.99
A−	***High-Yield Neuroanatomy***	Fix	Lippincott Williams & Wilkins, 2015, 208 pages	Review/ Test/50 q	$36.99
A−	***Anatomy—An Essential Textbook***	Gilroy	Thieme, 2013, 504 pages	Text/ Test/400 q	$44.99
A−	***Atlas of Anatomy***	Gilroy	Thieme, 2016, 760 pages	Text	$82.99
B+	***High-Yield Gross Anatomy***	Dudek	Lippincott Williams & Wilkins, 2014, 320 pages	Review	$39.99
B+	***Clinical Anatomy Made Ridiculously Simple***	Goldberg	MedMaster, 2012, 175 pages	Review	$29.95
B+	***PreTest Neuroscience***	Siegel	McGraw-Hill, 2013, 412 pages	Test/500 q	$39.00
B+	***Crash Course: Anatomy***	Sternhouse	Elsevier, 2015, 288 pages	Review	$44.99
B+	***Déjà Review: Neuroscience***	Tremblay	McGraw-Hill, 2010, 266 pages	Review	$25.00
B	***BRS Embryology***	Dudek	Lippincott Williams & Wilkins, 2014, 336 pages	Review/ Test/220 q	$51.99
B	***Anatomy Flash Cards: Anatomy on the Go***	Gilroy	Thieme, 2013, 565 flash cards	Flash cards	$59.99
B	***Clinical Neuroanatomy Made Ridiculously Simple***	Goldberg	MedMaster, 2014, 90 pages + CD-ROM	Review/Test/ Few q	$25.95

Anatomy, Embryology, and Neuroscience *(continued)*

		AUTHOR	PUBLISHER	TYPE	PRICE
B	***Rapid Review: Gross and Developmental Anatomy***	Moore	Elsevier, 2010, 304 pages	Review/Test/450 q	$42.95
B	***Case Files: Anatomy***	Toy	McGraw-Hill, 2014, 416 pages	Cases	$35.00
B	***Case Files: Neuroscience***	Toy	McGraw-Hill, 2014, 432 pages	Cases	$35.00
B$^-$	***Gray's Anatomy for Students Flash Cards***	Drake	Elsevier, 2014, 350 flash cards	Flash cards	$39.99
B$^-$	***Netter's Anatomy Flash Cards***	Hansen	Saunders, 2014, 674 flash cards	Flash cards	$39.95

Behavioral Science

		AUTHOR	PUBLISHER	TYPE	PRICE
A	***High-Yield Behavioral Science***	Fadem	Lippincott Williams & Wilkins, 2012, 144 pages	Review	$37.99
A$^-$	***BRS Behavioral Science***	Fadem	Lippincott Williams & Wilkins, 2016, 384 pages	Review/Test/700 q	$49.99
A$^-$	***High-Yield Biostatistics, Epidemiology, and Public Health***	Glaser	Lippincott Williams & Wilkins, 2013, 168 pages	Review	$42.99
A$^-$	***Clinical Biostatistics and Epidemiology Made Ridiculously Simple***	Weaver	MedMaster, 2011, 104 pages	Review	$22.95
B$^+$	***USMLE Medical Ethics***	Fischer	Kaplan, 2012, 216 pages	Cases	Variable
B$^+$	***Jekel's Epidemiology, Biostatistics, Preventive Medicine, and Public Health***	Katz	Saunders, 2013, 420 pages	Review/Test/477 q	$59.95

Biochemistry

		AUTHOR	PUBLISHER	TYPE	PRICE
A$^-$	***Lange Flash Cards Biochemistry and Genetics***	Baron	McGraw-Hill, 2013, 184 flash cards	Flash cards	$40.00
A$^-$	***Rapid Review: Biochemistry***	Pelley	Elsevier, 2010, 208 pages	Review/Test/350 q	$42.95
B$^+$	***Lippincott's Illustrated Reviews: Biochemistry***	Ferrier	Lippincott Williams & Wilkins, 2013, 560 pages	Review/Test/500 q	$75.99
B$^+$	***Déjà Review: Biochemistry***	Manzoul	McGraw-Hill, 2010, 206 pages	Review	$25.00
B$^+$	***Medical Biochemistry—An Illustrated Review***	Panini	Thieme, 2013, 441 pages	Review/Test/400 q	$39.99
B$^+$	***PreTest Biochemistry and Genetics***	Wilson	McGraw-Hill, 2013, 592 pages	Test/500 q	$38.00
B	***Clinical Biochemistry Made Ridiculously Simple***	Goldberg	MedMaster, 2010, 95 pages + foldout	Review	$24.95
B	***BRS Biochemistry, Molecular Biology, and Genetics***	Lieberman	Lippincott Williams & Wilkins, 2013, 432 pages	Review/Test	$51.99
B$^-$	***Case Files: Biochemistry***	Toy	McGraw-Hill, 2014, 480 pages	Cases	$35.00

Cell Biology and Histology

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁻	***High-Yield Cell and Molecular Biology***	Dudek	Lippincott Williams & Wilkins, 2010, 151 pages	Review	$37.99
B	***Elsevier's Integrated Review: Genetics***	Adkison	Elsevier, 2011, 272 pages	Review	$42.95
B	***BRS Cell Biology and Histology***	Gartner	Lippincott Williams & Wilkins, 2014, 432 pages	Review/Test/320 q	$49.99
B	***Crash Course: Cell Biology and Genetics***	Stubbs	Elsevier, 2015, 216 pages	Review	$46.99
B⁻	***Wheater's Functional Histology***	Young	Elsevier, 2013, 464 pages	Text	$82.95

Microbiology and Immunology

		AUTHOR	PUBLISHER	TYPE	PRICE
A	***Déjà Review: Microbiology & Immunology***	Chen	McGraw-Hill, 2010, 432 pages	Review	$25.00
A	***Clinical Microbiology Made Ridiculously Simple***	Gladwin	MedMaster, 2015, 400 pages	Review	$36.95
A	***Lange Microbiology & Infectious Diseases Flash Cards***	Somers	McGraw-Hill, 2010, 189 flash cards	Flash cards	$46.00
A⁻	***Basic Immunology***	Abbas	Elsevier, 2015, 352 pages	Review	$69.99
A⁻	***Microcards: Microbiology Flash Cards***	Harpavat	Lippincott Williams & Wilkins, 2015, 312 flash cards	Flash cards	$49.99
A⁻	***Medical Microbiology and Immunology Flash Cards***	Rosenthal	Elsevier, 2016, 384 flash cards	Flash cards	$39.99
B⁺	***Elsevier's Integrated Immunology and Microbiology***	Actor	Elsevier, 2011, Kindle edition	Review	$38.99
B⁺	***Lippincott's Illustrated Reviews: Immunology***	Doan	Lippincott Williams & Wilkins, 2012, 384 pages	Review/Test/Few q	$67.99
B⁺	***Lippincott's Illustrated Reviews: Microbiology***	Harvey	Lippincott Williams & Wilkins, 2012, 448 pages	Review/Test/Few q	$67.99
B⁺	***Review of Medical Microbiology and Immunology***	Levinson	McGraw-Hill, 2016, 832 pages	Review/Test/654 q	$64.00
B	***Case Studies in Immunology: Clinical Companion***	Geha	Garland Science, 2016, 358 pages	Cases	$59.00
B	***Pretest: Microbiology***	Kettering	McGraw-Hill, 2013, 480 pages	Test/500 q	$38.00
B	***Rapid Review: Microbiology and Immunology***	Rosenthal	Elsevier, 2010, 240 pages	Review/Test/400 q	$42.95
B	***Case Files: Microbiology***	Toy	McGraw-Hill, 2014, 416 pages	Cases	$36.00

Pathology

		AUTHOR	PUBLISHER	TYPE	PRICE
A⁺	***Pathoma: Fundamentals of Pathology***	Sattar	Pathoma, 2016, 218 pages	Review/Lecture	$82.95
A	***Rapid Review: Pathology***	Goljan	Elsevier, 2013, 784 pages	Review/Test/400 q	$55.95

Pathology *(continued)*

		AUTHOR	PUBLISHER	TYPE	PRICE
A–	***Lange Pathology Flash Cards***	Baron	McGraw-Hill, 2013, 300 flash cards	Flash cards	$41.00
A–	***Déjà Review: Pathology***	Davis	McGraw-Hill, 2010, 474 pages	Review	$25.00
A–	***Lippincott's Illustrated Q&A Review of Rubin's Pathology***	Fenderson	Lippincott Williams & Wilkins, 2010, 336 pages	Test/1000 q	$59.99
A–	***Robbins and Cotran Review of Pathology***	Klatt	Elsevier, 2014, 504 pages	Test/1100 q	$54.99
A–	***BRS Pathology***	Schneider	Lippincott Williams & Wilkins, 2013, 480 pages	Review/ Test/450 q	$51.99
A–	***Crash Course: Pathology***	Xiu	Elsevier, 2015, 356 pages	Review	$44.99
B	***PreTest Pathology***	Brown	McGraw-Hill, 2010, 612 pages	Test/500 q	$39.00
B	***High-Yield Histopathology***	Dudek	Lippincott Williams & Wilkins, 2016, 350 pages	Review	$35.99
B	***Pathophysiology of Disease: Introduction to Clinical Medicine***	McPhee	McGraw-Hill, 2014, 784 pages	Text	$80.00
B	***Haematology at a Glance***	Mehta	Blackwell Science, 2014, 136 pages	Review	$48.95
B	***Pocket Companion to Robbins and Cotran Pathologic Basis of Disease***	Mitchell	Elsevier, 2016, 896 pages	Review	$39.99

Pharmacology

		AUTHOR	PUBLISHER	TYPE	PRICE
A–	***Lange Pharmacology Flash Cards***	Baron	McGraw-Hill, 2013, 230 flash cards	Flash cards	$41.00
A–	***Master the Boards USMLE Step 1 Pharmacology Flashcards***	Fischer	Kaplan, 2015, 408 flash cards	Flash cards	$54.99
A–	***Déjà Review: Pharmacology***	Gleason	McGraw-Hill, 2010, 240 pages	Review	$25.00
A–	***Lippincott's Illustrated Reviews: Pharmacology***	Harvey	Lippincott Williams & Wilkins, 2014, 680 pages	Review/ Test/380 q	$71.99
A–	***Pharm Cards: Review Cards for Medical Students***	Johannsen	Lippincott Williams & Wilkins, 2010, 240 flash cards	Flash cards	$49.99
B+	***Crash Course: Pharmacology***	Battista	Elsevier, 2015, 236 pages	Review	$44.99
B+	***Pharmacology Flash Cards***	Brenner	Elsevier, 2012, 200 flash cards	Flash cards	$39.95
B+	***Elsevier's Integrated Pharmacology***	Kester	Elsevier, 2011, 264 pages	Review	$42.95
B+	***Rapid Review: Pharmacology***	Pazdernik	Elsevier, 2010, 360 pages	Review/ Test/450 q	$42.95
B+	***BRS Pharmacology***	Rosenfeld	Lippincott Williams & Wilkins, 2013, 384 pages	Review/ Test/200 q	$51.99
B	***PreTest Pharmacology***	Shlafer	McGraw-Hill, 2013, 624 pages	Test/500 q	$38.00
B	***Case Files: Pharmacology***	Toy	McGraw-Hill, 2013, 464 pages	Cases	$35.00
B	***Katzung & Trevor's Pharmacology: Examination and Board Review***	Trevor	McGraw-Hill, 2015, 592 pages	Review/ Test/1000 q	$54.00

Physiology

		AUTHOR	PUBLISHER	TYPE	PRICE
A^+	***BRS Physiology***	Costanzo	Lippincott Williams & Wilkins, 2014, 328 pages	Review/ Test/350 q	$53.99
A	***Acid-Base, Fluids, and Electrolytes Made Ridiculously Simple***	Preston	MedMaster, 2011, 156 pages	Review	$22.95
A^-	***Physiology***	Costanzo	Saunders, 2013, 520 pages	Text	$62.95
A^-	***Color Atlas of Physiology***	Silbernagl	Thieme, 2015, 472 pages	Review	$49.99
B^+	***BRS Physiology Cases and Problems***	Costanzo	Lippincott Williams & Wilkins, 2012, 368 pages	Cases	$51.99
B^+	***Déjà Review: Physiology***	Gould	McGraw-Hill, 2010, 298 pages	Review	$25.00
B^+	***PreTest Physiology***	Metting	McGraw-Hill, 2013, 528 pages	Test/500 q	$38.00
B	***Rapid Review: Physiology***	Brown	Elsevier, 2011, 288 pages	Test/350 q	$42.95
B	***Vander's Renal Physiology***	Eaton	McGraw-Hill, 2013, 224 pages	Text	$47.00
B	***Endocrine Physiology***	Molina	McGraw-Hill, 2013, 320 pages	Review	$50.00
B	***Netter's Physiology Flash Cards***	Mulroney	Saunders, 2015, 200+ flash cards	Flash cards	$39.99
B	***Pulmonary Pathophysiology: The Essentials***	West	Lippincott Williams & Wilkins, 2012, 208 pages	Review/ Test/50 q	$52.99

NOTES

SECTION IV

Abbreviations and Symbols

ABBREVIATION	MEANING
⊕	positive
⊖	negative
1°	primary
2°	secondary
3°	tertiary
1st MC*	1st metacarpal
A-a	alveolar-arterial [gradient]
AA	Alcoholics Anonymous, amyloid A
AAMC	Association of American Medical Colleges
Aao*	ascending aorta
Ab	antibody
ABP	androgen-binding protein
AC	adenylyl cyclase
ACA	anterior cerebral artery
Acetyl-CoA	acetyl coenzyme A
ACD	anemia of chronic disease
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
ACL	anterior cruciate ligament
ACom	anterior communicating [artery]
ACTH	adrenocorticotropic hormone
AD*	Alzheimer dementia
ADA	adenosine deaminase, Americans with Disabilities Act
ADH	antidiuretic hormone
ADHD	attention-deficit hyperactivity disorder
ADP	adenosine diphosphate
ADPKD	autosomal-dominant polycystic kidney disease
AFP	α-fetoprotein
Ag	antigen, silver
AICA	anterior inferior cerebellar artery
AIDS	acquired immunodeficiency syndrome
AIHA	autoimmune hemolytic anemia
AKT	protein kinase B
AL	amyloid light [chain]
ALA	aminolevulinate
ALL	acute lymphoblastic (lymphocytic) leukemia
ALP	alkaline phosphatase
α_1, α_2	sympathetic receptors
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase
AMA	American Medical Association, antimitochondrial antibody
AML	acute myelogenous (myeloid) leukemia
AMP	adenosine monophosphate
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
ANOVA	analysis of variance
ANP	atrial natriuretic peptide
ANS	autonomic nervous system
Ant*	anterior
anti-CCP	anti-cyclic citrullinated peptide
Ao*	aorta
AOA	American Osteopathic Association
AP	action potential, A & P [ribosomal binding sites]
APAF-1	apoptotic protease activating factor 1
APC	antigen-presenting cell, activated protein C
Apo	apolipoprotein
APP	amyloid precursor protein
APRT	adenine phosphoribosyltransferase
APSAC	anistreplase
aPTT	activated partial thromboplastin time
APUD	amine precursor uptake decarboxylase
AR	attributable risk, autosomal recessive, aortic regurgitation
ara-C	arabinofuranosyl cytidine (cytarabine)
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
Arg	arginine
ARMD	age-related macular degeneration
ARPKD	autosomal-recessive polycystic kidney disease
AS	aortic stenosis
ASA	anterior spinal artery
ASD	atrial septal defect
ASO	anti–streptolysin O
AST	aspartate transaminase
AT	angiotensin, antithrombin
ATCase	aspartate transcarbamoylase
ATN	acute tubular necrosis
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
ATTR	transthyretin-mediated amyloidosis
AV	atrioventricular
AZT	azidothymidine
β_1, β_2	sympathetic receptors
BAL	British anti-Lewisite [dimercaprol]
BCG	bacille Calmette-Guérin
BH_4	tetrahydrobiopterin
BIMS	Biometric Identity Management System

*Image abbreviation only

ABBREVIATION	MEANING
BM	basement membrane
BMI	body-mass index
BMR	basal metabolic rate
BOOP	bronchiolitis obliterans organizing pneumonia
BP	bisphosphate, blood pressure
BPG	bisphosphoglycerate
BPH	benign prostatic hyperplasia
BT	bleeding time
BUN	blood urea nitrogen
Ca*	capillary
Ca^{2+}	calcium ion
CAD	coronary artery disease
CAF	common application form
CALLA	common acute lymphoblastic leukemia antigen
cAMP	cyclic adenosine monophosphate
CBG	corticosteroid-binding globulin
Cbl	cobalamin
Cbm*	cerebellum
CBSE	Comprehensive Basic Science Examination
CBSSA	Comprehensive Basic Science Self-Assessment
CBT	computer-based test, cognitive behavioral therapy
CC*	corpus callosum
CCA*	common carotid artery
CCK	cholecystokinin
CCS	computer-based case simulation
CD	cluster of differentiation
CDK	cyclin-dependent kinase
cDNA	complementary deoxyribonucleic acid
CEA	carcinoembryonic antigen
CETP	cholesteryl-ester transfer protein
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CFX	circumflex [artery]
CGD	chronic granulomatous disease
cGMP	cyclic guanosine monophosphate
CGN	*cis*-Golgi network
C_H1–C_H3	constant regions, heavy chain [antibody]
ChAT	choline acetyltransferase
CHD*	common hepatic duct
χ^2	chi-squared
CI	confidence interval
CIN	candidate identification number, carcinoma in situ, cervical intraepithelial neoplasia
CIS	Communication and Interpersonal Skills
CK	clinical knowledge, creatine kinase
CK-MB	creatine kinase, MB fraction
C_L	constant region, light chain [antibody]
CL	clearance
Cl^-	chloride ion
CLL	chronic lymphocytic leukemia
CMC	carpometacarpal (joint)
CML	chronic myelogenous (myeloid) leukemia
CMV	cytomegalovirus
CN	cranial nerve

ABBREVIATION	MEANING
CN^-	cyanide ion
CNS	central nervous system
CNV	copy number variation
CO	carbon monoxide, cardiac output
CO_2	carbon dioxide
CoA	coenzyme A
COL1A1	collagen, type I, alpha 1
COL1A2	collagen, type I, alpha 2
COMT	catechol-O-methyltransferase
COOH	carboxyl group
COP	coat protein
COPD	chronic obstructive pulmonary disease
CoQ	coenzyme Q
COX	cyclooxygenase
C_p	plasma concentration
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CPR	cardiopulmonary resuscitation
Cr	creatinine
CRC	colorectal cancer
CREST	calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerosis, and telangiectasias [syndrome]
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CS	clinical skills
C-section	cesarean section
CSF	cerebrospinal fluid
CT	computed tomography
CTP	cytidine triphosphate
CVA	cerebrovascular accident
CVID	common variable immunodeficiency
CXR	chest x-ray
Cys	cysteine
DAF	decay-accelerating factor
DAG	diacylglycerol
dATP	deoxyadenosine triphosphate
DCIS	ductal carcinoma in situ
DCT	distal convoluted tubule
ddC	dideoxycytidine [zalcitabine]
ddI	didanosine
DES	diethylstilbestrol
DHAP	dihydroxyacetone phosphate
DHB	dihydrobiopterin
DHEA	dehydroepiandrosterone
DHF	dihydrofolic acid
DHS	Department of Homeland Security
DHT	dihydrotestosterone
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DIP	distal interphalangeal [joint]
DKA	diabetic ketoacidosis
DLCO	diffusing capacity for carbon monoxide
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DNR	do not resuscitate

*Image abbreviation only

ABBREVIATION	MEANING
dNTP	deoxynucleotide triphosphate
DO	doctor of osteopathy
DPGN	diffuse proliferative glomerulonephritis
DPM	doctor of podiatric medicine
DPP-4	dipeptidyl peptidase-4
DPPC	dipalmitoylphosphatidylcholine
DS	double stranded
dsDNA	double-stranded deoxyribonucleic acid
dsRNA	double-stranded ribonucleic acid
d4T	didehydrodeoxythymidine [stavudine]
dTMP	deoxythymidine monophosphate
DTR	deep tendon reflex
DTs	delirium tremens
dUDP	deoxyuridine diphosphate
dUMP	deoxyuridine monophosphate
DVT	deep venous thrombosis
E*	euthromatin, esophagus
EBV	Epstein-Barr virus
EC	ejection click
ECA*	external carotid artery
ECF	extracellular fluid
ECFMG	Educational Commission for Foreign Medical Graduates
ECG	electrocardiogram
ECL	enterochromaffin-like [cell]
ECM	extracellular matrix
ECT	electroconvulsive therapy
ED_{50}	median effective dose
EDRF	endothelium-derived relaxing factor
EDTA	ethylenediamine tetra-acetic acid
EDV	end-diastolic volume
EEG	electroencephalogram
EF	ejection fraction
EGF	epidermal growth factor
EHEC	enterohemorrhagic *E coli*
ELISA	enzyme-linked immunosorbent assay
EM	electron micrograph/microscopy
EMB	eosin–methylene blue
Epi	epinephrine
EPO	erythropoietin
EPS	extrapyramidal system
ER	endoplasmic reticulum, estrogen receptor
ERAS	Electronic Residency Application Service
ERCP	endoscopic retrograde cholangiopancreatography
ERP	effective refractory period
eRPF	effective renal plasma flow
ERT	estrogen replacement therapy
ERV	expiratory reserve volume
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ESV	end-systolic volume
ETEC	enterotoxigenic *E coli*
EtOH	ethyl alcohol
EV	esophageal vein
F	bioavailability

ABBREVIATION	MEANING
FA	fatty acid
Fab	fragment, antigen-binding
FAD	flavin adenine dinucleotide
FAD^+	oxidized flavin adenine dinucleotide
$FADH_2$	reduced flavin adenine dinucleotide
FAP	familial adenomatous polyposis
F1,6BP	fructose-1,6-bisphosphate
F2,6BP	fructose-2,6-bisphosphate
FBPase	fructose bisphosphatase
Fc	fragment, crystallizable
FcR	Fc receptor
5f-dUMP	5-fluorodeoxyuridine monophosphate
Fe^{2+}	ferrous ion
Fe^{3+}	ferric ion
Fem*	femur
FENa	excreted fraction of filtered sodium
FEV_1	forced expiratory volume in 1 second
FF	filtration fraction
FFA	free fatty acid
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FISH	fluorescence in situ hybridization
FKBP	FK506 binding protein
FLAIR	fluid-attenuated inversion recovery
f-met	formylmethionine
FMG	foreign medical graduate
FMN	flavin mononucleotide
FN	false negative
FNHTR	febrile nonhemolytic transfusion reaction
FP	false positive
F1P	fructose-1-phosphate
F6P	fructose-6-phosphate
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FSMB	Federation of State Medical Boards
FTA-ABS	fluorescent treponemal antibody—absorbed
FTD*	frontotemporal dementia
5-FU	5-fluorouracil
FVC	forced vital capacity
GABA	γ-aminobutyric acid
GAG	glycosaminoglycan
Gal	galactose
GBM	glomerular basement membrane
GC	glomerular capillary
G-CSF	granulocyte colony-stimulating factor
GERD	gastroesophageal reflux disease
GFAP	glial fibrillary acid protein
GFR	glomerular filtration rate
GGT	γ-glutamyl transpeptidase
GH	growth hormone
GHB	γ-hydroxybutyrate
GHRH	growth hormone–releasing hormone
G_I	G protein, I polypeptide
GI	gastrointestinal

*Image abbreviation only

ABBREVIATION	MEANING
GIP	gastric inhibitory peptide
GIST	gastrointestinal stromal tumor
GLUT	glucose transporter
GM	granulocyte macrophage
GM-CSF	granulocyte-macrophage colony stimulating factor
GMP	guanosine monophosphate
GnRH	gonadotropin-releasing hormone
GP	glycoprotein
G3P	glucose-3-phosphate
G6P	glucose-6-phosphate
G6PD	glucose-6-phosphate dehydrogenase
GPe	globus pallidus externa
GPi	globus pallidus interna
GPI	glycosyl phosphatidylinositol
GRP	gastrin-releasing peptide
G_S	G protein, S polypeptide
GS	glycogen synthase
GSH	reduced glutathione
GSSG	oxidized glutathione
GTP	guanosine triphosphate
GTPase	guanosine triphosphatase
GU	genitourinary
H^*	heterochromatin
H^+	hydrogen ion
H_1, H_2	histamine receptors
H_2S	hydrogen sulfide
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HAVAb	hepatitis A antibody
Hb	hemoglobin
Hb^+	oxidized hemoglobin
Hb^-	ionized hemoglobin
HBcAb	hepatitis B core antibody
HBcAg	hepatitis B core antigen
HBeAb	hepatitis B early antibody
HBeAg	hepatitis B early antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
$HbCO_2$	carbaminohemoglobin
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCO_3^-	bicarbonate
Hct	hematocrit
HCTZ	hydrochlorothiazide
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDV	hepatitis D virus
H&E	hematoxylin and eosin
HEV	hepatitis E virus
HF	heart failure
Hfr	high-frequency recombination [cell]
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HHb	human hemoglobin

ABBREVIATION	MEANING
HHV	human herpesvirus
5-HIAA	5-hydroxyindoleacetic acid
HIE	hypoxic ischemic encephalopathy
His	histidine
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HL	hepatic lipase
HLA	human leukocyte antigen
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HMP	hexose monophosphate
HMSN	hereditary motor and sensory neuropathy
HMWK	high-molecular-weight kininogen
HNPCC	hereditary nonpolyposis colorectal cancer
hnRNA	heterogeneous nuclear ribonucleic acid
H_2O	water
H_2O_2	hydrogen peroxide
HPA	hypothalamic-pituitary-adrenal [axis]
HPL	human placental lactogen
HPO	hypothalamic-pituitary-ovarian [axis]
HPV	human papillomavirus
HR	heart rate
HRE	hormone receptor element
HSV	herpes simplex virus
5-HT	5-hydroxytryptamine (serotonin)
HTLV	human T-cell leukemia virus
HTN	hypertension
HTR	hemolytic transfusion reaction
HUS	hemolytic-uremic syndrome
HVA	homovanillic acid
HZV	herpes zoster virus
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IC	inspiratory capacity, immune complex
I_{Ca}	calcium current [heart]
I_f	funny current [heart]
ICA	internal carotid artery
ICAM	intracellular adhesion molecule
ICD	implantable cardioverter defibrillator
ICE	Integrated Clinical Encounter
ICF	intracellular fluid
ICP	intracranial pressure
ID	identification
ID_{50}	median infective dose
IDL	intermediate-density lipoprotein
I/E	inspiratory/expiratory [ratio]
IF	immunofluorescence, initiation factor
IFN	interferon
Ig	immunoglobulin
IGF	insulin-like growth factor
I_K	potassium current [heart]
IL	interleukin
IM	intramuscular
IMA	inferior mesenteric artery
IMED	International Medical Education Directory

*Image abbreviation only

ABBREVIATION	MEANING
IMG	international medical graduate
IMP	inosine monophosphate
IMV	inferior mesenteric vein
I_{Na}	sodium current [heart]
INO	internuclear ophthalmoplegia
INR	International Normalized Ratio
IO	inferior oblique [muscle]
IOP	intraocular pressure
IP_3	inositol triphosphate
IPV	inactivated polio vaccine
IR	current × resistance [Ohm's law], inferior rectus [muscle]
IRV	inspiratory reserve volume
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUGR	intrauterine growth restriction
IV	intravenous
IVC	inferior vena cava
IVDU	intravenous drug use
IVIG	intravenous immunoglobulin
JAK/STAT	Janus kinase/signal transducer and activator of transcription [pathway]
JGA	juxtaglomerular apparatus
JVD	jugular venous distention
JVP	jugular venous pulse
K^+	potassium ion
KatG	catalase-peroxidase produced by *M tuberculosis*
K_e	elimination constant
K_f	filtration constant
KG	ketoglutarate
K_m	Michaelis-Menten constant
KOH	potassium hydroxide
L	left, liver
LA	left atrial, left atrium
LAD	left anterior descending coronary artery
LAF	left anterior fascicle
LAP	leukocyte alkaline phosphatase
Lat cond*	lateral condyle
Lb*	lamellar body
LCA	left coronary artery
LCAT	lecithin-cholesterol acyltransferase
LCC*	left common carotid artery
LCFA	long-chain fatty acid
LCL	lateral collateral ligament
LCME	Liaison Committee on Medical Education
LCMV	lymphocytic choriomeningitis virus
LCX	left circumflex coronary artery
LD	loading dose
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LES	lower esophageal sphincter
LFA	leukocyte function–associated antigen
LFT	liver function test
LGN	lateral geniculate nucleus

ABBREVIATION	MEANING
LGV	left gastric vein
LH	luteinizing hormone
LLQ	left lower quadrant
LM	light microscopy, left main coronary artery
LMN	lower motor neuron
LOS	lipooligosaccharide
LP	lumbar puncture
LPA*	left pulmonary artery
LPL	lipoprotein lipase
LPS	lipopolysaccharide
LR	lateral rectus [muscle]
LT	labile toxin leukotriene
LV	left ventricle, left ventricular
Lys	lysine
M_1-M_5	muscarinic (parasympathetic) ACh receptors
MAC	membrane attack complex, minimal alveolar concentration
MALT	mucosa-associated lymphoid tissue
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure, mitogen-activated protein
MASP	mannose-binding lectin–associated serine protease
Max*	maxillary sinus
MBL	mannose-binding lectin
MC	midsystolic click
MCA	middle cerebral artery
MCAT	Medical College Admissions Test
MCHC	mean corpuscular hemoglobin concentration
MCL	medial collateral ligament
MCP	metacarpophalangeal [joint]
MCV	mean corpuscular volume
MD	maintenance dose
Med cond*	medial condyle
MELAS syndrome	mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
MEN	multiple endocrine neoplasia
Mg^{2+}	magnesium ion
MGN	medial geniculate nucleus
$MgSO_4$	magnesium sulfate
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MI	myocardial infarction
MIF	müllerian inhibiting factor
MLCK	myosin light-chain kinase
MLF	medial longitudinal fasciculus
MMC	migrating motor complex
MMR	measles, mumps, rubella [vaccine]
6-MP	6-mercaptopurine
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
MPO-ANCA/p-ANCA	perinuclear antineutrophil cytoplasmic antibody
MR	medial rectus [muscle], mitral regurgitation
MRI	magnetic resonance imaging
miRNA	microribonucleic acid

*Image abbreviation only

ABBREVIATION	MEANING
mRNA	messenger ribonucleic acid
MRSA	methicillin-resistant *S aureus*
MS	mitral stenosis, multiple sclerosis
MSH	melanocyte-stimulating hormone
MSM	men who have sex with men
mtDNA	mitochondrial DNA
mtRNA	mitochondrial RNA
mTOR	mammalian target of rapamycin
MTP	metatarsophalangeal [joint]
MTX	methotrexate
MUA/P	Medically Underserved Area and Population
MVO$_2$	myocardial oxygen consumption
MVP	mitral valve prolapse
N*	nucleus
N/A	not applicable
Na$^+$	sodium ion
NAD	nicotinamide adenine dinucleotide
NAD$^+$	oxidized nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP$^+$	oxidized nicotinamide adenine dinucleotide phosphate
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NBME	National Board of Medical Examiners
NBOME	National Board of Osteopathic Medical Examiners
NBPME	National Board of Podiatric Medical Examiners
NC	no change
NE	norepinephrine
NF	neurofibromatosis
NFAT	nuclear factor of activated T-cell
NH$_3$	ammonia
NH$_4^+$	ammonium
NIDDM	non-insulin-dependent diabetes mellitus
NK	natural killer [cells]
N$_M$	muscarinic ACh receptor in neuromuscular junction
NMDA	N-methyl-D-aspartate
NMJ	neuromuscular junction
NMS	neuroleptic malignant syndrome
N$_N$	nicotinic ACh receptor in autonomic ganglia
NRMP	National Residency Matching Program
NNRTI	non-nucleoside reverse transcriptase inhibitor
NO	nitric oxide
N$_2$O	nitrous oxide
NPH	neutral protamine Hagedorn, normal pressure hydrocephalus
NPV	negative predictive value
NRI	norepinephrine receptor inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NSE	neuron-specific enolase
NSTEMI	non–ST-segment elevation myocardial infarction
Nu*	nucleolus
OAA	oxaloacetic acid
OCD	obsessive-compulsive disorder
OCP	oral contraceptive pill
OH	hydroxy

ABBREVIATION	MEANING
OH$_2$	dihydroxy
1,25-OH D$_3$	calcitriol (active form of vitamin D)
25-OH D$_3$	storage form of vitamin D
3′ OH	hydroxyl
OMT	osteopathic manipulative technique
OPV	oral polio vaccine
OR	odds ratio
OS	opening snap
OTC	ornithine transcarbamoylase
OVLT	organum vasculosum of the lamina terminalis
P-body	processing body (cytoplasmic)
P-450	cytochrome P-450 family of enzymes
PA	posteroanterior, pulmonary artery
PABA	*para*-aminobenzoic acid
Paco_2	arterial Pco_2
PAco_2	alveolar Pco_2
PAH	*para*-aminohippuric acid
PAN	polyarteritis nodosa
Pao_2	partial pressure of oxygen in arterial blood
PAo_2	partial pressure of oxygen in alveolar blood
PAP	Papanicolaou [smear], prostatic acid phosphatase
PAPPA	pregnancy-associated plasma protein A
PAS	periodic acid–Schiff
Pat*	patella
PBP	penicillin-binding protein
PC	plasma colloid osmotic pressure, platelet count, pyruvate carboxylase
PCA	posterior cerebral artery
PCL	posterior cruciate ligament
Pco_2	partial pressure of carbon dioxide
PCom	posterior communicating [artery]
PCOS	polycystic ovarian syndrome
PCP	phencyclidine hydrochloride, *Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PCT	proximal convoluted tubule
PCWP	pulmonary capillary wedge pressure
PD	posterior descending [artery]
PDA	patent ductus arteriosus, posterior descending artery
PDC	pyruvate dehydrogenase complex
PDE	phosphodiesterase
PDGF	platelet-derived growth factor
PDH	pyruvate dehydrogenase
PE	pulmonary embolism
PECAM	platelet–endothelial cell adhesion molecule
PEco_2	expired air Pco_2
PEP	phosphoenolpyruvate
PF	platelet factor
PFK	phosphofructokinase
PFT	pulmonary function test
PG	phosphoglycerate
P$_i$	plasma interstitial osmotic pressure, inorganic phosphate
PICA	posterior inferior cerebellar artery
PID	pelvic inflammatory disease

*Image abbreviation only

ABBREVIATION	MEANING
PIO_2	Po_2 in inspired air
PIP	proximal interphalangeal [joint]
PIP_2	phosphatidylinositol 4,5-bisphosphate
PIP_3	phosphatidylinositol 3,4,5-bisphosphate
PKD	polycystic kidney disease
PKR	interferon-α–induced protein kinase
PKU	phenylketonuria
PLP	pyridoxal phosphate
PLS	Personalized Learning System
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear [leukocyte]
P_{net}	net filtration pressure
PNET	primitive neuroectodermal tumor
PNS	peripheral nervous system
Po_2	partial pressure of oxygen
PO_4	salt of phosphoric acid
PO_4^{3-}	phosphate
Pop*	popliteal artery
Pop a*	popliteal artery
Post*	posterior
PPAR	peroxisome proliferator-activated receptor
PPD	purified protein derivative
PPI	proton pump inhibitor
PPV	positive predictive value
PR3-ANCA/ c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
PrP	prion protein
PRPP	phosphoribosylpyrophosphate
PSA	prostate-specific antigen
PSS	progressive systemic sclerosis
PT	prothrombin time
PTH	parathyroid hormone
PTHrP	parathyroid hormone–related protein
PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
PV	plasma volume, venous pressure
Pv*	pulmonary vein
PVC	polyvinyl chloride
PVR	pulmonary vascular resistance
R	correlation coefficient, right, R variable [group]
R_3	Registration, Ranking, & Results [system]
RA	right atrium
RAAS	renin-angiotensin-aldosterone system
RANK-L	receptor activator of nuclear factor-κ B ligand
RAS	reticular activating system
RBC	red blood cell
RBF	renal blood flow
RCA	right coronary artery
REM	rapid eye movement
RER	rough endoplasmic reticulum
Rh	*rhesus* antigen
RLQ	right lower quadrant
RNA	ribonucleic acid
RNP	ribonucleoprotein

ABBREVIATION	MEANING
ROS	reactive oxygen species
RPF	renal plasma flow
RPGN	rapidly progressive glomerulonephritis
RPR	rapid plasma reagin
RR	relative risk, respiratory rate
rRNA	ribosomal ribonucleic acid
RS	Reed-Sternberg [cells]
RSC*	right subclavian artery
RSV	respiratory syncytial virus
RTA	renal tubular acidosis
RUQ	right upper quadrant
RV	residual volume, right ventricle, right ventricular
RVH	right ventricular hypertrophy
Rx	medical prescription
[S]	substrate concentration
SA	sinoatrial
SAA	serum amyloid–associated [protein]
SAM	S-adenosylmethionine
SARS	severe acute respiratory syndrome
SAT	Scholastic Aptitude Test
SC	subcutaneous
SCC	squamous cell carcinoma
SCD	sudden cardiac death
SCID	severe combined immunodeficiency disease
SCJ	squamocolumnar junction
SCM	sternocleidomastoid muscle
SCN	suprachiasmatic nucleus
SD	standard deviation
SE	standard error of the mean
SEP	Spoken English Proficiency
SER	smooth endoplasmic reticulum
SERM	selective estrogen receptor modulator
SGLT	sodium-glucose transporter
SHBG	sex hormone–binding globulin
SIADH	syndrome of inappropriate [secretion of] antidiuretic hormone
SIDS	sudden infant death syndrome
SLE	systemic lupus erythematosus
SLL	small lymphocytic lymphoma
SLT	Shiga-like toxin
SMA	superior mesenteric artery
SMX	sulfamethoxazole
SNARE	soluble NSF attachment protein receptor
SNc	substantia nigra pars compacta
SNP	single nucleotide polymorphism
SNr	substantia nigra pars reticulata
SNRI	serotonin and norepinephrine receptor inhibitor
snRNP	small nuclear ribonucleoprotein
SO	superior oblique [muscle]
SOAP	Supplemental Offer and Acceptance Program
Sp*	spleen
spp	species
SR	superior rectus [muscle]
SS	single stranded

*Image abbreviation only

ABBREVIATION	MEANING
ssDNA	single-stranded deoxyribonucleic acid
SSPE	subacute sclerosing panencephalitis
SSRI	selective serotonin reuptake inhibitor
ssRNA	single-stranded ribonucleic acid
St*	stomach
ST	Shiga toxin
StAR	steroidogenic acute regulatory protein
STEMI	ST-segment elevation myocardial infarction
STI	sexually transmitted infection
STN	subthalamic nucleus
SV	splenic vein, stroke volume
SVC	superior vena cava
SVT	supraventricular tachycardia
$t_{1/2}$	half-life
T_3	triiodothyronine
T_4	thyroxine
TAPVR	total anomalous pulmonary venous return
TB	tuberculosis
TBG	thyroxine-binding globulin
3TC	dideoxythiacytidine [lamivudine]
TCA	tricarboxylic acid [cycle], tricyclic antidepressant
Tc cell	cytotoxic T cell
TCR	T-cell receptor
TDF	tenofovir disoproxil fumarate
TdT	terminal deoxynucleotidyl transferase
TE	tracheoesophageal
TFT	thyroid function test
TG	triglyceride
TGA	*trans*-Golgi apparatus
TGF	transforming growth factor
TGN	*trans*-Golgi network
Th cell	helper T cell
THF	tetrahydrofolic acid
TI	therapeutic index
TIA	transient ischemic attack
Tib*	tibia
TIBC	total iron-binding capacity
TIPS	transjugular intrahepatic portosystemic shunt
TLC	total lung capacity
T_m	maximum rate of transport
TMP	trimethoprim
TN	true negative
TNF	tumor necrosis factor
TNM	tumor, node, metastases [staging]
ToRCHeS	*Toxoplasma gondii*, rubella, CMV, HIV, HSV-2, syphilis
TP	true positive
tPA	tissue plasminogen activator
TPO	thyroid peroxidase, thrombopoietin
TPP	thiamine pyrophosphate
TPR	total peripheral resistance
TR	tricuspid regurgitation
TRAP	tartrate-resistant acid phosphatase
TRH	thyrotropin-releasing hormone

ABBREVIATION	MEANING
tRNA	transfer ribonucleic acid
TSH	thyroid-stimulating hormone
TSI	triple sugar iron
TSS	toxic shock syndrome
TSST	toxic shock syndrome toxin
TTP	thrombotic thrombocytopenic purpura
TTR	transthyretin
TV	tidal volume
Tx	translation [factor]
TXA_2	thromboxane A_2
UDP	uridine diphosphate
UMN	upper motor neuron
UMP	uridine monophosphate
UPD	uniparental disomy
URI	upper respiratory infection
USMLE	United States Medical Licensing Examination
UTI	urinary tract infection
UTP	uridine triphosphate
UV	ultraviolet
$\dot{V}_1$, $\dot{V}_2$	Vasopressin receptors
VC	vital capacity
V_d	volume of distribution
VD	physiologic dead space
V(D)J	heavy-chain hypervariable region [antibody]
VDRL	Venereal Disease Research Laboratory
VEGF	vascular endothelial growth factor
V_H	variable region, heavy chain [antibody]
VHL	von Hippel-Lindau [disease]
VIP	vasoactive intestinal peptide
VIPoma	vasoactive intestinal polypeptide-secreting tumor
VJ	light-chain hypervariable region [antibody]
VL	ventral lateral [nucleus]; variable region, light chain [antibody]
VLDL	very low density lipoprotein
VMA	vanillylmandelic acid
VMAT	vesicular monoamine transporter
V_{max}	maximum velocity
VPL	ventral posterior nucleus, lateral
VPM	ventral posterior nucleus, medial
VPN	vancomycin, polymyxin, nystatin [media]
$\dot{V}/\dot{Q}$	ventilation/perfusion [ratio]
VRE	vancomycin-resistant enterococcus
VSD	ventricular septal defect
V_T	tidal volume
vWF	von Willebrand factor
VZV	varicella-zoster virus
WBC	white blood cell
VMAT	vesicular monoamine transporter
XR	X-linked recessive
XX	normal complement of sex chromosomes for female
XY	normal complement of sex chromosomes for male
ZDV	zidovudine [formerly AZT]

*Image abbreviation only

SECTION IV

Image Acknowledgments

In this edition, in collaboration with MedIQ Learning, LLC, and a variety of other partners, we are pleased to include the following clinical images and diagrams for the benefit of integrative student learning.

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Biochemistry

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45 **Cilia structure: Image C.** Dextrocardia. This image is a derivative work, adapted from the following source, available under CC BY: Oluwadare O, Ayoka AO, Akomolafe RO, et al. The role of electrocardiogram in the diagnosis of dextrocardia with mirror image atrial arrangement and ventricular position in a young adult Nigerian in Ile-Ife: a case report. *J Med Case Rep* 2015;9:222. doi 10.1186/s13256-015-0695-4.

47 **Osteogenesis imperfecta: Image A.** Skeletal deformities in lower body of child. This image is a derivative work, adapted from the following source, available under CC BY: Vanakker OM, Hemelsoet D, De Paepe. Hereditary connective tissue diseases in young adult stroke: a comprehensive synthesis. *Stroke Res Treat* 2011;712903. doi 10.4061/2011/712903. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

47 **Osteogenesis imperfecta: Image B.** Skeletal deformities in upper extremity of child. This image is a derivative work, adapted from the following source, available under CC BY: Vanakker OM, Hemelsoet D, De Paepe. Hereditary connective tissue diseases in young adult stroke: a comprehensive synthesis. *Stroke Res Treat* 2011;712903. doi 10.4061/2011/712903. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

47 **Osteogenesis imperfecta: Image C.** Blue sclera. This image is a derivative work, adapted from the following source, available under CC BY-SA. Courtesy of Fred H, van Dijk H. Images of memorable cases: cases 40, 41 & 42. Connexions Web site. December 3, 2008. Available at: http://cnx.org/content/m15020/1.3/. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY-SA.

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51 **Fluorescence in situ hybridization: Image A.** This image is a derivative work, adapted from the following source, available under CC BY: Paar C, Herber G, Voskova, et al. A case of acute myeloid leukemia (AML) with an unreported combination of chromosomal abnormalities: gain of isochromosome 5p, tetrasomy 8 and unbalanced translocation der(19)t(17;19)(q23;p13). *Mol Cytogenet* 2013;6:40. doi 10.1186/1755-8166-6-40.

57 **Muscular dystrophies.** Fibrofatty replacement of muscle. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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67 **Marasmus: Image B.** Child with marasmus. Courtesy of the US Department of Health and Human Services.

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81 **Cystinuria.** Hexagonal stones in urine. This image is a derivative work, adapted from the following source, available under : Courtesy of Cayla Devine.

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Immunology

94 **Sinusoids of spleen.** Red and white pulp. This image is a derivative work, adapted from the following source, available under : Heinrichs S, Conover LF, Bueso-Ramos CE, et al. MYBL2 is a sub-haploinsufficient tumor suppressor gene in myeloid malignancy. *eLife* 2013;2:e00825. doi 10.7554/eLife.00825. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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113 **Ataxia-telangiectasia: Image A.** Spider angioma (telangiectasia). This image is a derivative work, adapted from the following source, available under : Liapakis IE, Englander M, Sinani R, et al. Management of facial telangiectasias with hand cautery. *World J Plast Surg* 2015 Jul; 4(2):127-133.

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Microbiology

122 **Stains: Image A.** *Trypanosoma lewisi* on Giemsa stain. Courtesy of the US Department of Health and Human Services and Dr. Mae Melvin.

122 **Stains: Image B.** *Tropheryma whipplei* on periodic acid–Schiff stain. This image is a derivative work, adapted from the following source, available under : Dr. Ed Uthman.

122 **Stains: Image C.** *Mycobacterium tuberculosis* on Ziehl-Neelsen stain. Courtesy of the US Department of Health and Human Services and Dr. George P. Kubica.

122 **Stains: Image D.** *Cryptococcus neoformans* on India ink stain. Courtesy of the US Department of Health and Human Services.

122 **Stains: Image E.** *Coccidioides immitis* on silver stain. Courtesy of the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.

124 **Encapsulated bacteria.** Capsular swelling of *Streptococcus pneumoniae* using the Neufeld-Quellung test. Courtesy of the US Department of Health and Human Services.

124 **Catalase-positive organisms: Image A.** Oxygen bubbles released during catalase reaction. This image is a derivative work, adapted from the following source, available under . Courtesy of Stefano Nase. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under .

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CJ, Tracy B. The transcriptional program underlying the physiology of clostridial sporulation. *Genome Biol* 2008;9:R114. doi 10.1186/gb-2008-9-7-r114.

131 **α-hemolytic bacteria: Image A.** α-hemolysis. This image is a derivative work, adapted from the following source, available under CC BY-SA. Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY-SA.

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132 ***Streptococcus pneumoniae.*** PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Mike Miller.

132 ***Streptococcus pyogenes:* Image A. (group A streptococci)**. Gram stain. This image is a derivative work, adapted from the following source, available under CC BY-SA. Courtesy of Y. Tambe. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY-SA.

133 ***Bacillus anthracis.*** Ulcer with black eschar. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and James H. Steele.

134 **Clostridia (with exotoxins): Image A.** Gas gangrene due to *Clostridium perfringens* infection. This image is a derivative work, adapted from the following source, available under CC BY: Courtesy of Engelbert Schröpfer, Stephan Rauthe, and Thomas Meyer.

134 **Clostridia (with exotoxins): Image B.** Pseudomembranous enterocolitis on colonoscopy. This image is a derivative work, adapted from the following source, available under CC BY-SA. Courtesy of Klinikum Dritter Orden für die Überlassung des Bildes zur Veröffentlichu. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY-SA.

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135 ***Nocardia* vs *Actinomyces*: Image B.** *Actinomyces israelii* on Gram stain. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

136 **Mycobacteria.** Acid-fast stain. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.

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139 ***Pseudomonas aeruginosa:* Image A.** Blue-green pigment. This image is a derivative work, adapted from the following source, available under CC BY-SA. Courtesy of Hansen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY-SA.

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140 ***Klebsiella.*** PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

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142 ***Helicobacter pylori.*** PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services, Dr. Patricia Fields, and Dr. Collette Fitzgerald.

142 **Spirochetes.** Dark-field microscopic appearance. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

142 **Lyme disease: Image A.** *Ixodes* tick. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Michael L. Levin.

142 **Lyme disease: Image B.** Erythema migrans. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and James Gathany.

143 **Syphilis: Image A.** Painless chancre in 1° syphilis. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and M. Rein.

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143 **Syphilis: Image E.** Condyloma lata. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Susan Lindsley.

143 **Syphilis: Image F.** Gumma. This image is a derivative work, adapted from the following source, available under CC BY: Chakir K, Benchikhi H. Granulome centro-facial révélant une syphilis tertiaire. *Pan Afr Med* J 2013;15:82. doi 10.11604/pamj.2013.15.82.3011.

143 **Syphilis: Image G.** Congenital syphilis. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Norman Cole.

143 **Syphilis: Image H.** Hutchinson teeth. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Susan Lindsley.

144 ***Gardnerella vaginalis.*** PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and M. Rein.

145 **Rickettsial diseases and vector-borne illnesses: Image A.** Rash of Rocky Mountain spotted fever. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

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147 **Systemic mycoses: Image A.** *Histoplasma*. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. D.T. McClenan.

147 **Systemic mycoses: Image B.** *Blastomyces dermatitidis* undergoing broad-base budding. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Libero Ajello.

147 **Coccidioidomycosis: Image C.** Coccidiomycosis with endospheres. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

147 **Systemic mycoses: Image D.** "Captain's wheel" shape of *Paracoccidioides*. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Lucille K. Georg.

148 **Cutaneous mycoses: Image G.** Tinea versicolor. This image is a derivative work, adapted from the following source, available under CC BY SA. Courtesy of Sarah (Rosenau) Korf. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY SA.

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149 **Opportunistic fungal infections: Image C.** Oral thrush. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Sol Silverman, Jr.

149 **Opportunistic fungal infections: Image E.** Conidiophores of *Aspergillus fumigatus*. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

149 **Opportunistic fungal infections: Image F.** *Cryptococcus neoformans*. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Leanor Haley.

149 **Opportunistic fungal infections: Image G.** *Cryptococcus neoformans* on mucicarmine stain. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Leanor Haley.

149 **Opportunistic fungal infections: Image H.** Mucor. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Lucille K. Georg.

150 ***Pneumocystis jirovecii:* Image A.** Interstitial opacities in lung. This image is a derivative work, adapted from the following source, available under CC BY: Chuang C, Zhanhong X, Yinyin G, et al. Unsuspected *Pneumocystis pneumonia* in an HIV-seronegative patient with untreated lung cancer: circa case report. *J Med Case Reports* 2007;1:15. doi 10.1186/1752-1947-1-115.

150 ***Pneumocystis jirovecii:* Image B.** Ground-glass opacities on CT. This image is a derivative work, adapted from the following source, available under CC BY: Oikonomou A and Prassopoulos P. Mimics in chest disease: interstitial opacities. Insights Imaging 2013;4:9-27. doi 0.1007/s13244-012-0207-7. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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151 **Protozoa—GI infections: Image B.** *Giardia lamblia* cyst. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

151 **Protozoa—GI infections: Image C.** *Entamoeba histolytica* trophozoites. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

151 **Protozoa—GI infections. Image D.** *Entamoeba histolytica* cyst. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

151 **Protozoa—GI infections: Image E.** *Cryptosporidium* oocysts. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

152 **Toxoplasma gondii: Image A.** MRI toxoplasma. This image is a derivative work, adapted from the following source, available under cc BY: Agrawal A, Bhake A, Sangole VM, et al. Multiple-ring enhancing lesions in an immunocompetent adult. *J Glob Infect Dis* 2010 Sep-Dec; 2(3):313-4. doi 10.4103/0974-777X.68545.

152 **Protozoa—CNS infections: Image B.** *Toxoplasma gondii* tachyzoite. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. L.L. Moore, Jr.

152 **Protozoa—CNS infections: Image C.** *Naegleria fowleri* amoebas. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

152 **Protozoa—CNS infections: Image D.** *Trypanosoma brucei gambiense.* PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Mae Melvin.

153 **Protozoa—hematologic infections: Image A.** *Plasmodium* trophozoite ring form. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

153 **Protozoa—hematologic infections: Image B.** *Plasmodium* schizont containing merozoites. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Steven Glenn.

153 **Protozoa—hematologic infections: Image C.** *Babesia.* PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

154 **Protozoa—others: Image A.** Trypanosoma cruzi. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Mae Melvin.

154 **Protozoa—others: Image B.** Leishmania donovani. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Francis W. Chandler. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

154 **Protozoa—others: Image C.** *Trichomonas vaginalis.* PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

155 **Nematodes (roundworms): Image A.** *Enterobius vermicularis* eggs. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services, B.G. Partin, and Dr. Moore.

155 **Nematodes (roundworms): Image B.** *Ascaris lumbricoides* egg. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

155 **Nematodes (roundworms): Image C.** Elephantiasis. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

156 **Cestodes (tapeworms): Image A.** *Taenia solium* scolex. This image is a derivative work, adapted from the following source, available under cc BY SA. Courtesy of Robert J. Galindo. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under cc BY SA.

156 **Trematodes (flukes): Image A.** *Schistosoma mansoni* egg with lateral spine. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

156 **Cestodes (tapeworms): Image B.** Neurocysticercosis. This image is a derivative work, adapted from the following source, available under cc BY: Coyle CM, Tanowitz HB. Diagnosis and treatment of neurocysticercosis. *Interdiscip Perspect Infect Dis* 2009;2009:180742. doi 10.1155/2009/180742. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

156 **Trematodes (flukes): Image B.** *Schistosoma mansoni* egg with terminal spine. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

156 **Echinococcus granulosus: Image C.** PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

156 **Cestodes (tapeworms): Image D.** Gross specimen of a hyatid cyst of *Echinococcus granulosus.* PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. I. Kagan.

156 **Cestodes (tapeworms): Image E.** *Echinococcus granulosus* cyst in liver. This image is a derivative work, adapted from the following source, available under cc BY: Ma Z, Yang W, Yao Y, et al. The adventitia resection in treatment of liver hydatid cyst: a case report of a 15-year-old boy. *Case Rep Surg* 2014;2014:123149. doi 10.1155/2014/123149.

157 **Ectoparasites: Image A.** Scabies. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and J. Pledger.

157 **Ectoparasites: Image B.** Lice. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Joe Miller

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160 **Herpesviruses: Image B.** Herpes labialis. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Herrmann.

160 **Herpesviruses: Image E.** Shingles (varicella-zoster virus infection). This image is a derivative work, adapted from the following source, available under cc BY SA. Courtesy of Fisle. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under cc BY SA.

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160 **Herpesviruses: Image G.** Atypical lymphocytes in Epstein-Barr virus infection. This image is a derivative work, adapted from the following source, available under cc BY: Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

160 **Herpesviruses: Image I.** Roseola. PUBLIC DOMAIN Courtesy of Emiliano Burzagli.

160 **Herpesvirus: Image J.** Kaposi sarcoma. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

162 **HSV identification: Image A.** Positive Tzanck smear in HSV-2 infection. This image is a derivative work, adapted from the following source, available under cc BY SA. Courtesy of Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under cc BY SA.

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165 **Rubella virus.** Rubella rash. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

165 **Measles (rubeola) virus: Image A.** Koplik spots. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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165 **Measles (rubeola) virus: Image B.** Rash of measles. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

166 **Croup (acute laryngotracheobronchitis).** Steeple sign. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.

167 **Rabies virus: Image A.** Transmission electron micrograph. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services, Dr. Fred Murphy, and Sylvia Whitfield.

167 **Ebola virus.** PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Cynthia Goldsmith.

167 **Rabies virus: Image B.** Negri bodies. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Daniel P. Perl.

176 **Osteomyelitis: Images A and B.** This image is a derivative work, adapted from the following source, available under cc BY: Pandey V, Rao SP, Rao S, et al. *Burkholderia pseudomallei* musculoskeletal infections (melioidosis) in India. *Indian J Orthop* 2010;44:216-220. doi 10.4103/0019-5413.61829.

177 **Common vaginal infections: Image C.** *Candida* vulvovaginitis. PUBLIC DOMAIN Courtesy of Mikael Häggström.

178 **ToRCHeS infections: Image A.** "Blueberry muffin" rash. This image is a derivative work, adapted from the following source, available under cc BY: Benmiloud S, Elhaddou G, Belghiti ZA, et al. Blueberry muffin syndrome. *Pan Afr Med* J 2012;13:23. PMCID: PMC3527055.

178 **ToRCHeS infections: Image B.** Periventricular calcifications in congenital cytomegalovirus infection. This image is a derivative work, adapted from the following source, available under cc BY: Bonthius D, Perlman S. Congenital viral infections of the brain: lessons learned from lymphocytic choriomeningitis virus in the neonatal rat. PLoS Pathog 2007;3:e149. doi 10.1371/journal.ppat.0030149. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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Pathology

205 **Necrosis: Image A.** Coagulative necrosis. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Dr. Steven Rosenberg.

205 **Necrosis: Image B.** Liquefactive necrosis. PUBLIC DOMAIN Courtesy of Daftblogger.

205 **Necrosis: Image C.** Caseous necrosis. This image is a derivative work, adapted from the following source, available under cc BY SA. Courtesy of Dr. Yale Rosen. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under cc BY SA.

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205 **Necrosis: Image F.** Acral gangrene. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and William Archibald.

206 **Ischemia: Image A.** Cortical watershed area. This image is a derivative work, adapted from the following source, available under cc BY: Isabel C, Lecler A, Turc G, et al. Relationship between watershed infarcts and recent intra plaque haemorrhage in carotid atherosclerotic plaque. *PLoS One* 2014;9(10):e108712. doi 10.1371/journal.pone.0108712.

207 **Infarcts: red vs. pale: Image B.** Pale infarct. Courtesy of Armed Forces Institute of Pathology.

208 **Types of calcification: Image A.** Dystrophic calcification. This image is a derivative work, adapted from the following source, available under cc BY: Chun J-S, Hong R, Kim J-A. Osseous metaplasia with mature bone formation of the thyroid gland: three case reports. *Oncol Lett* 2013;6:977-979. doi 10.3892/

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210 **Scar formation: Image B.** Keloid scar. This image is a derivative work, adapted from the following source, available under CC BY-SA. Courtesy of Dr. Andreas Settje. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY-SA.

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213 **Amyloidosis: Image A.** Amyloid deposits on Congo red stain. This image is a derivative work, adapted from the following source, available under CC BY: Dr. Ed Uthman.

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215 **Neoplastic progression: Image A.** Cervical tissue. This image is a derivative work, adapted from the following source, available under CC BY: Dr. Ed Uthman. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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Pharmacology

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Cardiology

271 **Coronary artery anatomy: Image A.** This image is a derivative work, adapted from the following source, available under CC BY: Zhang J, Chen L, Wang X, et al. Compounding local invariant features and global deformable geometry for medical image registration. *PLoS One* 2014;9(8):e105815. doi 10.1371/journal.pone.0105815.

288 **Congenital heart diseases: Image A.** Tetralogy of Fallot. This image is a derivative work, adapted from the following source, available under CC BY: Rashid AKM: Heart diseases in Down syndrome. In: Dey S, ed: Down syndrome. doi 10.5772/46009. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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288 **Congenital heart diseases: Image D.** Clubbing of fingers. PUBLIC DOMAIN Courtesy of Ann McGrath.

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296 **Myocardial infarction complications: Image B.** Drawing of pseudoaneurysm. This image is a derivative work, adapted from the following source, available under CC BY: Patrick J. Lynch and Dr. C. Carl Jaffe.

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297 **Cardiomyopathies: Image A.** Dilated cardiomyopathy. This image is a derivative work, adapted from the following source, available under CC BY: Gho JMIH, van Es R, Stathonikos N, et al. High resolution systematic digital histological quantification of cardiac fibrosis and adipose tissue in phospholamban p.Arg14del mutation associated cardiomyopathy. *PLoS One* 2014;9:e94820. doi 10.1371/journal.pone.0094820.

298 **Heart failure.** Pedal edema. This image is a derivative work, adapted from the following source, available under CC BY SA. Courtesy of Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY SA.

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302 **Vasculitides: Image B.** Angiogram in patient with Takayasu arteritis. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and Justin Ly.

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302 **Vasculitides: Image D.** Strawberry tongue in patient with Kawasaki disease. This image is a derivative work, adapted from the following source, available under CC BY: Natr.

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302 **Vasculitides: Image G.** Granulomatosis with polyangiitis (formerly Wegener) and PR3-ANCA/c-ANCA. PUBLIC DOMAIN Courtesy of M.A. Little.

302 **Vasculitides: Image H.** Microscopic polyangiitis and MPO-ANCA/p-ANCA. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services and M.A. Little.

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Endocrine

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325 **Neuroblastoma: Image B.** Neuroblastoma, Homer-Write rosettes. Courtesy of Dr. Kristine Krafts.

326 **Pheochromocytoma.** This image is a derivative work, adapted from the following source, available under CC BY: Dr. Michael Feldman.

328 **Hashimoto thyroiditis: Image A.** Hashimoto thyroiditis, Hurthle cells. Courtesy of Dr. Kristine Krafts.

328 **Hypothyroidism: Image B.** Before and after treatment of congenital hypothyroidism. PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

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329 **Hyperthyroidism: Image B.** Scalloped colloid. Courtesy of Dr. Kristine Krafts.

330 **Thyroid adenoma: Image A.** Courtesy of Dr. Kristine Krafts.

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338 **Carcinoid syndrome.** Carcinoid tumor histology. Courtesy of Armed Forces Institute of Pathology.

Gastrointestinal

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345 **Pancreas and spleen embryology.** Annular pancreas. This image is a derivative work, adapted from the following source, available under CC BY: Mahdi B, Selim S, Hassen T, et al. A rare cause of proximal intestinal obstruction in adults—annular pancreas: a case report. *Pan Afr Med J* 2011;10:56. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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360 **Esophageal pathologies: Image C.** Esophageal varices on CT. This image is a derivative work, adapted from the following source, available under CC BY-SA. Courtesy of Hellerhoff. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY-SA.

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366 **Appendicitis: Image A.** Fecalith. This image is a derivative work, adapted from the following source, available under CC BY-SA. Courtesy of Dr. James Heilman. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY-SA.

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374 Alcoholic liver disease: Image B. Mallory bodies. This image is a derivative work, adapted from the following source, available under CC BY-SA. Courtesy of Dr. Michael Bonert. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY-SA.

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Hematology and Oncology

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388 **Lymphocyte: Image A.** Lymphocyte with small amount of cytoplasm. This image is a derivative work, adapted from the following source, available under CC BY: Fickleandfreckled.

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394 **Pathologic RBC forms: Image B.** Basophilic stippling. This image is a derivative work, adapted from the following source, available under CC BY: van Dijk HA, Fred HL. Images of memorable cases: case 81. Connexions Web site. December 3, 2008. Available at http://cnx.org/contents/3196bf3e-1e1e-4c4d-a1ac-d4fc9ab65443@4@4.

394 **Pathologic RBC forms: Image C.** Dacrocyte ("teardrop cell"). Courtesy of Dr. Kristine Krafts.

394 **Pathologic RBC forms: Image D.** Degmacyte ("bite cell"). Courtesy of Dr. Kristine Krafts.

394 **Pathologic RBC forms: Image E.** Echinocyte ("burr cell"). Courtesy of Dr. Kristine Krafts.

394 **Pathologic RBC forms: Image F.** Elliptocyte. Courtesy of Dr. Kristine Krafts.

394 **Pathologic RBC forms: Image G.** Macro-ovalocyte. Courtesy of Dr. Kristine Krafts.

394 **Pathologic RBC forms: Image H.** Ringed sideroblast. This image is a derivative work, adapted from the following source, available under CC BY SA. Courtesy of Paulo Henrique Orlandi Mourao. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY SA.

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394 **Pathologic RBC forms: Image K.** Spherocyte. Courtesy of Dr. Kristine Krafts.

394 **Pathologic RBC forms: Image L.** Target cell. Courtesy of Dr. Kristine Krafts.

395 **Other RBC pathologies: Image A.** Heinz bodies. Courtesy of Dr. Kristine Krafts.

395 **Howell-Jolly bodies: Image B.** This image is a derivative work, adapted from the following source, available under CC BY: Serio B, Pezzullo L, Giudice V, et al. OPSI threat in hematological patients. *Transl Med UniSa* 2013 May-Aug; 6:2-10.

396 **Microcytic (MCV < 80 fL), hypochromic anemia: Image C.** β-thalassemia. Courtesy of Dr. Kristine Krafts.

396 **Microcytic (MCV < 80 fL), hypochromic anemia: Image D.** Lead lines in lead poisoning. Reproduced, with permission, from Dr. Frank Gaillard and www.radiopaedia.org.

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401 **Extrinsic hemolytic anemia: Image A.** Autoimmune hemolytic anemia. Courtesy of Dr. Kristine Krafts.

403 **Heme synthesis, porphyrias, and lead poisoning.** Basophilic stippling in lead poisoning. This image is a derivative work, adapted from the following source, available under CC BY: van Dijk HA, Fred HL. Images of memorable cases: case 81. Connexions Web site. December 3, 2008. Available at http://cnx.org/contents/3196bf3e-1e1e-4c4d-a1ac-d4fc9ab65443@4@4.

403 **Porphyria cutanea tarda: Image A.** Porphyria cutanea tarda. This image is a derivative work, adapted from the following source, available under CC BY: Bovenschen HJ, Vissers WHPM. Primary hemochromatosis presented by porphyria cutanea tarda: a case report. *Cases J* 2009;2:7246. doi 10.4076/1757-1626-2-7246.

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408 **Primary central nervous system lymphoma: Image C.** This image is a derivative work, adapted from the following source, available under CC BY: Mansour A, Qandeel M, Abdel-Razeq H, et al. MR imaging features of intracranial primary CNS lymphoma in immune competent patients. *Cancer Imaging* 2014;14(1):22. doi 10.1186/1470-7330-14-22.

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409 **Multiple myeloma: Image B.** RBC rouleaux formation. Courtesy of Dr. Kristine Krafts.

409 **Multiple myeloma: Image C.** Plasma cells. This image is a derivative work, adapted from the following source, available under CC BY: Sharma A, Kaushal M, Chaturvedi NK, et al. Cytodiagnosis of multiple myeloma presenting as orbital involvement: a case report. *Cytojournal* 2006;3:19. doi 10.1186/1742-6413-3-19.

410 **Leukemias: Image C.** Hairy cell leukemia. Courtesy of Dr. Kristine Krafts.

410 **Leukemias: Image E.** Chronic myelogenous leukemia. Courtesy of Dr. Kristine Krafts.

411 **Chronic myeloproliferative disorders: Image A.** Erythromelalgia in polycythemia vera. This image is a derivative work, adapted from the following source, available under CC BY: Fred H, van Dijk H. Images of memorable cases: case 151. Connexions Web site. December 4, 2008. Available at http://cnx.org/content/m14932/1.3/.

411 **Chronic myeloproliferative disorders: Image B.** Essential thrombocytosis with enlarged megakaryocytes. Courtesy of Dr. Kristine Krafts.

411 **Chronic myeloproliferative disorders: Image C.** Myelofibrosis. This image is a derivative work, adapted from the following source, available under CC BY: Dr. Ed Uthman.

411 **Chronic myeloproliferative disorders: Image D.** Dacrocyte ("teardrop cell"). Courtesy of Dr. Kristine Krafts.

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Musculoskeletal, Skin, and Connective Tissue

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424 **Myelin: Image A.** Myelinated neuron. PUBLIC DOMAIN Courtesy of the Electron Microscopy Facility at Trinity College.

424 **Common fractures: Image B.** Buckle fracture. This image is a derivative work, adapted from the following source, available under CC BY: Randsborg PH, Sivertsen EA. Classification of distal radius fractures in children: good inter- and intraobserver reliability, which improves with clinical experience. *BMC Musculoskelet Disord* 2012;13:6. doi 10.1186/1471-2474-13-6.

425 **Common knee conditions: Image A.** ACL tear. This image is a derivative work, adapted from the following source, available under CC BY: Chang MJ, Chang CB, Choi J-Y, et al. Can magnetic resonance imaging findings predict the degree of knee joint laxity in patients undergoing anterior cruciate ligament reconstruction? *BMC Musculoskelet Disord* 2014;15:214. doi 10.1186/1471-2474-15-214. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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433 **Muscle conduction to contraction: Image A.** Human skeletal muscle. PUBLIC DOMAIN Courtesy of Louisa Howard. The image may have been modified by cropping, labeling, and/or captions. All rights to this adaptation by MedIQ Learning, LLC are reserved.

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436 **Osteomalacia/rickets: Image B.** This image is a derivative work, adapted from the following source, available under CC BY: Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect* 2014;3:R13-R30. doi 10.1530/EC-13-0103.

436 **Paget disease of bone (osteitis deformans): Image A.** Thickened calvarium. This image is a derivative work, adapted from the following source, available under CC BY: Dawes L. Paget's disease. [Radiology Picture of the Day Website]. Published June 21, 2007. Available at http://www.radpod.org/2007/06/21/pagets-disease/.

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440 **Calcium pyrophosphate deposition disease: Image A.** This image is a derivative work, adapted from the following source, available under CC BY: Hahn M, Raithel M, Hagel A, et al. Chronic calcium pyrophosphate crystal inflammatory arthritis induced by extreme hypomagnesemia in short bowel syndrome. *BMC Gastroenterol* 2012;12:129. doi 10.1186/1471-230X-12-129.

440 **Gout: Image B.** Uric acid crystals under polarized light. This image is a derivative work, adapted from the following source, available under CC BY SA. Courtesy of Robert J. Galindo. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY SA.

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442 **Seronegative spondyloarthropathies: Image C, right.** Bamboo spine. PUBLIC DOMAIN Courtesy of Heather Hawker.

443 **Systemic lupus erythematosus: Image B.** Discoid rash. Courtesy of Dr. Kachiu Lee.

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495 **Neurocutaneous disorders: Image G.** Lisch nodules in neurofibromatosis. 🅮 Courtesy of the US Department of Health and Human Services.

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507 **Retinal detachment: Image A.** Courtesy of EyeRounds.

508 **Retinitis pigmentosa: Image A.** Courtesy of EyeRounds.

508 **Retinitis: Image A.** PUBLIC DOMAIN Courtesy of the US Department of Health and Human Services.

510 **Ocular motility.** Testing ocular muscles. This image is a derivative work, adapted from the following source, available under CC BY SA. Courtesy of Au.yousef. The image may have been modified by cropping, labeling, and/or captions. MedIQ Learning, LLC makes this image available under CC BY SA.

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Renal

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564 **Membranoproliferative glomerulonephritis (MPGN): Image E.** Membranoproliferative glomerulonephritis with “tram tracks” appearance on H&E stain. Courtesy of Dr. Adam Weinstein.

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Reproductive

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Index

A

Abacavir, 197, 199
Abciximab, 118
  Glycoprotein IIb/IIIa inhibitors, 415
  thrombogenesis and, 393
Abdominal aorta, **348**
  atherosclerosis in, 292, 668
  bifurcation of, 629
Abdominal aortic aneurysm, 292
Abdominal colic
  lead poisoning, 397
Abdominal distension
  duodenal atresia and, 344
Abdominal pain
  Budd-Chiari syndrome, 375, 652
  cilostazol/dipyridamole, 415
  Clostridium difficile, 652
  diabetic ketoacidosis and, 337
  ectopic pregnancy, 607
  Henoch-Schönlein purpura, 303, 655
  hypercalcemia, 560
  hyperparathyroidism, 332
  intussusception, 368
  irritable bowel syndrome, 366
  McBurney sign, 656
  Meckel diverticulum, 585
  pancreas divisum, 345
  pancreatic cancer, 380
  panic disorder, 533
  polyarteritis nodosa, 302
  porphyria, 403
  Rovsing sign, 656
Abdominal wall defects, 344
Abducens (CN VI), **476**
  location in brain stem, 474
  ocular motility and, 510
  palsy of, 511
Abducens nerve (CN VI), **476**
  ocular motility, 510
  palsy of, 511
  pathway for, 476
  ventral brain stem, 474
Abductor digiti minimi muscle, 429
Abductor pollicis brevis muscle, 429
Abetalipoproteinemia, 89, 394
Abnormal passive abduction, 424
Abnormal passive adduction, 424
ABO blood classification, 390
ABO hemolytic disease (newborn), **390**
Abscess, 451
Absence seizures, 487
  drug therapy for, 514
  treatment, 661
Absolute risk reduction (ARR), 248, 669
Absorption disorders and anemia, 396
AB toxin, 128
Abuse
  confidentiality exceptions, 255
  dependent personality disorder and, 535
  intimate partner violence, 257
Acalculia, 481
Acamprosate
  alcoholism, 541, 661
  diarrhea, 240
Acanthocytes, 394
Acanthocytosis, 66
Acantholysis, 448
  pemphigus vulgaris and, 452
Acanthosis, 448
  psoriasis, 449
Acanthosis nigricans, 217, 453
  acanthosis and, 448
  stomach cancer, 362
Acarbose, 341
  diarrhea, 240
Accessory (CN XI), **476**
  lesion in, 502
  location in brain stem, 474
Accessory nerve (CN XII), **476**
  lesion in, 502
  pathway for, 476
  ventral brain stem, 474
Accessory pancreatic duct, 345, 353
Accuracy vs precision, **249**
Acebutolol, 237
  angina and, 305
ACE inhibitors, **577**
  acute coronary syndromes, 296
  C1 esterase inhibitor deficiency, 103
  dilated cardiomyopathy, 297
  dry cough, 242
  heart failure, 298
  hypertension, 304
  naming convention for, 244
  preload/afterload effects, 273
  teratogenicity, 582
Acetaldehyde, 68
Acetaldehyde dehydrogenase, 68
Acetaminophen, **455**
  vs aspirin for pediatric patients, 455
  free radical injury and, 210
  hepatic necrosis from, 240
  for osteoarthritis, 439
  tension headaches, 488
  toxicity effects, 455
  toxicity treatment for, 239
Acetazolamide, 243, **575**
  glaucoma, 521
  metabolic acidosis, 561
  in nephron physiology, **555**
  pseudotumor cerebri, 491
  site of action, 574
Acetoacetate metabolism, 86
Acetone breath, 337
Acetylation, 41
  chromatin, 32
  posttranslation, 41
Acetylcholine (ACh)
  anticholinesterase effect on, 232
  change with disease, 465
  in nervous system, 229
  opioid analgesics, **520**
  pacemaker action potential and, 281
Acetylcholine (ACh) receptor agonists, 520
Acetylcholine (ACh) receptors, **229**
  in cholinergic drugs, 231
Acetylcholine (AChR) receptor, 217
Acetylcholinesterase (AChE)
  cholinesterase inhibitor poisoning, 232
  malathion, 196
  neural tube defects and, 461
Acetylcholinesterase (AChE) inhibitors
  Alzheimer disease, 518
  in cholinergic drugs, 231
  myasthenia gravis, 445
  naming convention for, 244
  toxicity treatment for, 239
Acetyl-CoA carboxylase
  fatty acid synthesis, 69
  vitamin B_7 and, 64
Achalasia, **360**
  esophageal cancer and, 361
Achilles reflex
  lumbosacral radiculopathy, 432
Achilles tendon xanthomas, 291, 652
Achlorhydria
  stomach cancer, 362
  VIPomas, 356
Achondroplasia, **435**
  chromosome disorder, 60
  endochondral ossification in, 434
  inheritance, 56
AChR (acetylcholine receptor), 217
Acid-base physiology, **561**
Acidemia, 561
  diuretic effect on, 576
Acidic amino acids, 77
Acid maltase, 82
Acidosis, **561**
  contractility in, 273
  hyperkalemia with, 560
Acid phosphatase in neutrophils, 386
Acid reflux
  esophageal pathology and, 360
  H_2 blockers for, 381
  proton pump inhibitors for, 381
Acid suppression therapy, **381**
Acinetobacter spp
  nosocomial infections, 181
  taxonomy, 121
Acinetobacter baumannii
  highly resistant bacteria, 194
Acne, 449
  danazol, 622
  PCOS, 609
  skin papules, 447
  tetracyclines for, 188
Acoustic schwannomas, 652
Acquired hydroceles, 618
Acrodermatitis enteropathica, 67
Acromegaly, **333**
  GH, 317
  octreotide for, 382
  somatostatin analogs for, 315
  somatostatin for, 342
Acromion, 425
ACTH. *See* Adrenocorticotropic hormone (ACTH)
Actin
  cytoskeleton, 44
  muscular dystrophies, 57
Actin filaments
  epithelial cells, 447
  muscle contraction, 433
Acting out, 524
Actinic keratosis, 453
  associations of, 664
  squamous cell carcinoma, 454

Actinomyces spp
  anaerobic organism, 123
  Gram-positive algorithm, 130
  Nocardia spp vs, 135
  penicillin G/V for, 183
Actinomyces israelii
  labs/findings, 657
  oral infections, 182
  pigment production, 125
Action/willpower, 539
Activated carriers, **71**
Activator proteins, 38
Active errors, 262
Active immunity, **107**
Acute chest syndrome, 400
Acute cholestatic hepatitis
  as drug reaction, 240
  macrolides, 189
Acute coronary syndrome
  ADP receptor inhibitors for, 415
  heparin for, 413
  nitrates for, 305
  treatments for, **296**
Acute cystitis, 562
Acute disseminated encephalomyelitis, 494
Acute dystonia, 233
Acute gastritis, 362
Acute glomerulonephritis, 571
Acute hemolytic transfusion reactions, 110
Acute hemorrhagic cystitis, 160
Acute inflammation, 207
Acute inflammatory demyelinating polyradiculopathy, **493**
Acute intermittent porphyria, 403
Acute interstitial nephritis, **572**
Acute lymphoblastic leukemia (ALL), **410**
  associations with, 664
  methotrexate for, 417
  oncogenes and, 218
Acute mesenteric ischemia, 369
  presentation, 655
Acute myelogenous leukemia (AML), **410**
  chromosomal translocations, 412
  cytarabine for, 417
  myelodysplastic syndromes, 409
Acute myeloid leukemia (AML)
  associations with, 664
Acute pancreatitis, **380**
  associations, 667
  DIC and, 665
  hyperparathyroidism, 332
  necrosis and, 205
Acute pericarditis, **300**
Acute-phase proteins, 104
Acute-phase reactants, **102**
  IL-6, 104
Acute poststreptococcal glomerulonephritis, 564
Acute promyelocytic leukemia
  all-*trans* retinoic acid for, 62
  treatment, 661
Acute pulmonary edema
  opiod analgesics, 520
Acute pyelonephritis, 570
  labs/findings, 661
  renal papillary necrosis and, 572
  WBC casts in, 562
Acute renal failure, 571
Acute respiratory distress syndrome (ARDS), **642**
  acute pancreatitis, 380
  eclampsia and, 608
  inhalational injury, 640
Acute stress disorder, 534
Acute transplant rejection, 115
Acute tubular necrosis, **572**
  granular casts in, 562
  intrinsic renal failure with, 571
Acyclovir, **197**
Adalimumab, 118, 457
  for Crohn disease, 365
Adaptive immunity, **95**
Addison disease, 324
  metabolic acidosis in, 561
  presentation, 656
Additive drug interactions, 225
Adductor longus muscle, 353
Adenine
  methylation of, 32
  Shiga/Shiga-like toxins and, 128
Adenocarcinomas
  carcinogens causing, 219
  esophagus, 361
  gallbladder, 379
  gastrointestinal, 217
  lungs, 647
  nomenclature for, 216
  nonbacterial thrombotic endocarditis and, 217
  pancreas, 353, **380**
  pectinate line and, 351
  prostatic, 619
  stomach, 362, 665
Adenohypophysis, 313
  embryologic derivatives, 581
  hypothalamus and, 466
Adenomas
  bone, 437
  colorectal, 372
  nomenclature for, 216
  pituitary, 332
  primary hyperparathyroidism, 331
  salivary gland, 359
  thyroid, 330
Adenomatous colonic polyps, 370
Adenomyosis (endometrial), 612
Adenopathy
  Kawasaki disease, 302
  Whipple disease, 656
Adenosine
  as antiarrhythmic drug, 310
  cutaneous flushing, 239
  pacemaker action potential and, 281
Adenosine deaminase deficiency, **34**, 113
Adenosine triphosphate (ATP)
  in electron transport chain, 74
  in glycogen regulation, 81
  nephron physiology, 555
  production of, **71**, 74
  in TCA cycle, 73
  in urea cycle, 78
Adenosine triphosphate (ATP) synthase inhibitors, 74
Adenoviruses
  characteristics of, 160
  conjunctivitis, 504
  pneumonia, 645
  viral envelope, 159
  watery diarrhea, 175
Adherens junctions, 447
Adhesions, 369
Adipose lipolysis, 306
Adipose stores
  fasting/starvation states, 87
Adipose tissue
  estrogen production, 595
Adjustment disorder, 533
Adoption studies, **246**
ADP receptor inhibitors, **415**
ADP ribosyltransferases, 128
Adrenal adenomas
  Cushing syndrome, 323
  hyperaldosteronism, 324
Adrenal carcinomas
  Cushing syndrome, 323
  P-glycoprotein in, 220
Adrenal cortex, **312**
  embryologic derivatives, 581
  progesterone production, 595
Adrenal hemorrhage, 652
  Waterhouse-Friderichsen syndrome, 324
Adrenal hyperplasia
  Cushing syndrome, 323
  hyperaldosteronism and, 324
Adrenal insufficiency, **324**
  anovulation with, 609
  fludrocortisone for, 342
  vitamin B_5 deficiency, 63
Adrenal medulla, **312**
  innervation, 229
  neuroblastomas of, 325
  pheochromocytomas in, 326
  tumors, 668
Adrenal steroids, **318**
Adrenocortical adenomas, 665
Adrenocortical atrophy
  Addison disease, 324
  exogeneous corticosteroids, 323
Adrenocortical insufficiency
  as drug reaction, 240
  presentation, 656
Adrenocorticotropic hormone (ACTH)
  adrenal cortex regulation of, 312
  adrenal insufficiency and, 324
  in Cushing syndrome, 217, 323
  secretion of, 313
  signaling pathways of, 322
Adrenoleukodystrophy, **494**
Adrenoreceptors, 231
Adults
  common causes of death, 260
Adult T-cell leukemia, 219
Adult T-cell lymphoma, 408
Advance directives, 255
Aedes mosquitoes
  yellow fever transmission, 164
Aerobic metabolism
  ATP production, 71
  fed state, 87
  Vitamin B_1 (thiamine), 62
Aerobic organisms
  culture requirements, **123**
Afferent arteriole, 550
  ANP/BNP effect on, 558
  constriction of, 553
  dopamine effects, 559
  filtration, 553
Afferent nerves, 285
Aflatoxin
  as carcinogen, 219
  hepatocellular carcinoma, 375
Aflatoxins, 149
African sleeping sickness, 152
Afterload
  auscultation and, 278
  cardiac output, 273
  hydralazine, 304
  in shock, 299
Agammaglobulinemia
  chromosome affected, 60
Agars (bacterial culture), 123
Age-related macular degeneration, **506**
Aggregatibacter actinomycetemcomitans, 299
Aging changes, 259
Agnosia, 529
Agonist potency and efficacy, 228
Agoraphobia, 533
Agranulocytosis
  clozapine, 543
  as drug reaction, 241
  epilepsy drugs, 514
  sulfa drug allergies, 243
  thionamides, 341
Agraphia, 481
AIDS (acquired immunodeficiency syndrome)
  bacillary angiomatosis, 450
  brain abscess, 176
  Candida albicans, 149
  cryptococcal meningitis, 195
  Cryptosporidium, 151
  Cytomegalovirus (CMV), 161
  diagnosis, 171
  human herpesvirus 8, 161
  labs/findings, 660
  marijuana for, 541
  mycobacteria, 136
  Pneumocystis jirovecii, **150**
  primary central nervous system lymphoma (PCL), 408
  progressive multifocal leukoencephalopathy, 494
  retinitis, 161
  retroviruses, 163
  timecouse (untreated), 172
  Toxoplasma gondii, 152
AIDS retinitis, 161
Air emboli, 637

- Akathisia, 468, 489
- Akinesia, 490
- Akinesia in Parkinson disease, 655
- ALA dehydratase in lead poisoning, 403
- Alanine
  - ammonia transport, 78
  - pyruvate dehydrogenase complex deficiency, 73
- Alanine aminotransferase (ALT), 73, 373
- Alar plate, 460
- Albendazole
  - cestodes, 156
- Albinism, 448
  - catecholamine synthesis, 79
  - Chédiak-Higashi syndrome and, 113
  - locus heterogeneity, 53
  - ocular, 56
- Albright hereditary osteodystrophy, 331
- Albumin
  - acute-phase reactant, 102
  - calcium and, 319
  - as liver marker, 373
  - plasma volume and, 551
- Albuminuria
  - glomerular filtration barrier, 551
- Albuterol, 234
  - asthma, 649
- Alcohol dehydrogenase
  - ethanol metabolism, 68
- Alcohol exposure
  - in utero, 290
- Alcoholic cirrhosis, 374
  - cholelithiasis and, 379
  - zinc deficiency, 67
- Alcoholic hallucinosis, 542
- Alcoholic hepatitis, 374
- Alcoholic liver disease, **374**
- Alcoholism, **541**
  - anemia, 398
  - in anemia taxonomy, 396
  - cardiomyopathy, 297
  - cataracts and, 505
  - cirrhosis caused by, 372
  - common organisms affecting, 175
  - cytochrome P-450 and, 243
  - delirium tremens, 542
  - esophageal cancer, 361
  - ethanol metabolism and, 68
  - folate deficiency, 398
  - gastritis in, 362
  - hepatitis, 352
  - hypertension and, 290
  - ketone bodies in, 86
  - *Klebsiella* in, 140
  - Korsakoff syndrome, 528
  - liver serum markers in, 373
  - lung abscesses and, 646
  - magnesium levels in, 320
  - Mallory-Weiss syndrome in, 360
  - osteonecrosis in, 436
  - osteoporosis and, 435
  - pancreatitis, 240, 380
  - porphyria, 403
  - sideroblastic anemia, 397
  - subdural hematomas, 483
  - treatment, 661
  - vitamin B_1 deficiency, 62
  - vitamin B_9 deficiency, 64
  - wet beriberi, 653
- Alcohol-related disorders
  - readmissions with, 261
- Alcohol use
  - essential tremor, 489
  - gout and, 440
  - head and neck cancer, 636
  - intoxication and withdrawal, 540
  - loss of orientation, 528
  - sexual dysfunction, 537
  - sleep, 467
  - suicide and, 532
  - teratogenic effects, 582
- Alcohol withdrawal
  - benzodiazepines, 528
  - drug therapy, 542
  - hallucinations in, 529
- Aldesleukin, 117
- Aldolase B, 76
- Aldose reductase, 77
- Aldosterone, 558
  - adrenal cortex secretion of, 312
  - Gitelman syndrome as cause, 556
  - kidney effects, 559
  - nephron physiology, 555
  - primary adrenal insufficiency, 324
  - renal tubular acidosis, 562
  - SIADH, 334
  - signaling pathways for, 322
  - syndrome of apparent mineralocorticoid excess, 556
- Aldosterone antagonists, 304
- Aldosterone synthase, 318
- Alemtuzumab, 118
- Alendronate, 456
- Alirocumab, 306
- Aliskiren, **577**
- Alkalemia, 561
  - diuretic effects, 576
- Alkaline phosphatase (ALP), 373, 436
  - bone disorder lab values, 437
  - hyperparathyroidism and, 332
  - Paget disease of bone, 436
  - in thyroid storm, 329
  - as tumor marker, 220
- Alkalosis, **561**
  - bulimia nervosa, 537
  - hypokalemia with, 560
- Alkaptonuria, **80**
  - tyrosine catabolism and, 79
- *ALK* gene, 218
  - lung cancer, 647
- Alkylating agents, **418**
  - as carcinogens, 219
  - in cell cycle, 416
  - targets of, 416
  - teratogenicity of, 582
- Allantois, 585
- Allelic heterogeneity, **53**
- Allergic bronchopulmonary aspergillosis, 149
- Allergic contact dermatitis, 449
- Allergic reaction
  - blood transfusion, 110
- Allergic rhinitis, 449
- Allergies, 108
- Allografts, 114
- Allopurinol
  - for gout, 440, 457
  - gout, 661
  - kidney stones, 567
  - Lesch-Nyhan syndrome, 34
  - rash with, 241
- All-*trans* retinoic acid
  - acute promyelocytic leukemia, 62, 661
- Alopecia
  - doxorubicin, 418
  - etoposide/teniposide, 419
  - minoxidil for, 623
  - syphilis, 143
  - tinea capitis, 148
  - vitamin A toxicity, 62
  - vitamin B_5 deficiency, 63
  - vitamin B_7 deficiency, 64
- α-1,4-glucosidase
  - glycogen metabolism, 82
- α_1-antagonists
  - benign prostatic hyperplasia, 661
  - BPH treatment, 619
  - naming convention for, 244
- α_1-antitrypsin
  - elastin and, 48
- α_1-antitrypsin deficiency, 375
  - emphysema, 638
- α_2-agonists, **235**
- α_2-antagonists, 546
- α-adrenergic agonists, 648
- α-agonists, 521
- α-amanitin
  - RNA polymerase inhibition, 38
- α-amylase, 358
- α-antagonists
  - for pheochromocytomas, 326
  - pheochromocytomas, 663
- α-blockers, **236**
  - Beers criteria, 238
  - for cocaine overdose, 540
- α cells, 313
  - glucagonomas in, 338
  - glucagon production by, 315
- α-dystroglycan
  - muscular dystrophy, 57
- α-fetoprotein
  - anencephaly, 657
  - ataxia-telangiectasia, 113
  - autosomal trisomies, 59
  - in hepatocellular carcinoma, 375
  - neural tube defects, 461
  - spina bifida, 657
  - as tumor marker, 220
  - yolk sac tumors, 618
- α-galactosidase A
  - Fabry disease, 84
- α-glucosidase inhibitors, 341
- α-hemolytic bacteria, 131
- α-ketoglutarate
  - hyperammonemia and, 78
- α-ketoglutarate dehydrogenase
  - metabolic pathways, 70
  - TCA cycle, 73
  - vitamin B_1 and, 62
- α-methyldopa, 235
  - anemia and, 401
  - gestational hypertension, 608
- α-synuclein, 490
- α-thalassemia, 396
  - chromosome association, 60
- α toxin, 129, 134
- Alport syndrome, 565
  - cataracts and, 505
  - collagen deficiency in, 46
  - inheritance of, 55
  - presentation, 654
- Alprazolam, 515
- ALT (alanine transaminase)
  - hepatitis viruses, 168
  - toxic shock syndrome, 131
- Alteplase, 391, 415
- Alternative hypothesis, 251, 252
- Altitude sickness, 635
  - acetazolamide for, 575
- Altruism, 525
- Aluminum hydroxide, 382
- Alveolar gas equation, **634**, 670
- Alveolar period (development), 626
- Alveolar PO_2, 634
- Alveolar sacs, 628
- Alveolar ventilation, 630
- Alveoli, 626
  - pneumocytes, 627
- Alzheimer disease, 490
  - amyloidosis in, 213
  - dementia with, 529
  - Down syndome and, 59
  - drug therapy for, 232, **518**
  - labs/findings, 660, 665
  - neurotransmitters for, 465
  - ventriculomegaly with, 492
- *Amanita phalloides*
  - necrosis caused by, 240
  - RNA polymerase inhibition, 38
- Amantadine, 197, 517
- Ambiguous genitalia
  - 46,XY DSD, 604
  - ovotesticular disorder of sex development, 603
  - placental aromatase deficiency, 604
- Amebiasis, 151
- Amenorrhea
  - anorexia nervosa, 537
  - antiandrogens, 623
  - cirrhosis, 372
  - Cushing syndrome, 323
  - cystic fibrosis, 56
  - ectopic pregnancy and, 607
  - menopause, 600
  - Müllerian agenesis, 589
  - PCOS, 609
  - pituitary prolactinomas, 315
  - Turner syndrome, 603
- Amide local anesthetics, 519
- Amikacin, 183, 187
- Amiloride, 576
  - for diabetes insipidus, 334
  - nephron physiology, 555

- Amine precursor uptake decarboxylase (APUD), 325
- Amines
  - MAO inhibitors, 546
- Amine whiff test, 144
- Amino acids
  - blood-brain barrier and, 466
  - branched, 80
  - classification of, 77
  - derivatives of, **79**
  - genetic code for, 34
  - in histones, 32
  - ketogenic, 73
  - metabolism, 86
  - purine and pyrimidine synthesis, 33
  - tRNA, 40
  - urea cycle, 78
- Aminoaciduria
  - normal pregnancy, 554
- Aminoacyl-tRNA, 41
- Aminoacyl-tRNA synthase, 40
- Aminocaproic acid
  - for thrombolytic toxicity, 415
- Aminoglycosides, **187**
  - acute tubular necrosis, 572
  - magnesium levels and, 320
  - mechanism (diagram), 183
  - pregnancy use, 201
  - *Pseudomonas aeruginosa*, 139, 663
  - teratogenicity, 582
  - toxicity of, 242
- Aminopenicillins
  - mechanism and use, 184
- Amiodarone, 309
  - cytochrome P-450 and, 243
  - hypothyroidism, 240
  - hypothyroidism with, 328
  - photosensitivity, 241
  - pulmonary fibrosis, 242
  - restrictive lung disease, 639
- Amitriptyline, 545
  - migraine headaches, 488
  - tension headaches, 488
- Amlodipine, 304
- Ammonia
  - Ornithine transcarbamylase deficiency, 79
  - transport and intoxication, **78**
- Ammonium chloride
  - for drug overdoses, 226
- Amnesia
  - brain lesions, 481
  - classification of, 528
  - clinical drug-induced, 515, 519
  - electroconvulsive therapy, **528**
- Amnionitis, 135
- Amniotic fluid abnormalities, **607**
- Amniotic fluid emboli, 637
- Amniotic fluid embolism, 637
  - acute respiratory distress syndrome as cause, **642**
- Amoxapine, 545
- Amoxicillin
  - clinical use, 184
  - *Haemophilus influenzae*, 138
  - *Helicobacter pylori*, 142
  - Lyme disease, 142
  - mechanism (diagram), 183
  - prophylaxis, 194
- Amphetamines, 234
  - intoxication and withdrawal, 540
  - narcolepsy treatment, 538
  - as noradrenergic drug, 231
  - norepinephrine and, 231
  - pulmonary arterial hypertension, 643
  - as weak bases, 226
- Amphotericin B, 194
  - *Candida albicans*, 149, 661
  - clinical use, **195**
  - *Naegleria fowleri*, 152
  - opportunistic fungal infections, 149
  - systemic mycoses, 147
- Ampicillin
  - *Clostridium difficile*, 134
  - endometritis, 612
  - *Listeria monocytogenes*, 135
  - mechanism and use, 184
  - mechanism (diagram), 183
  - meningitis, 176
  - prophylaxis, 194
- Ampulla of Vater, 353
- Amygdaloid lesions, 481
- Amylase in pancreatitis, 380
- Amylin analogs, 341
- Amyloid angiopathy
  - intraparenchymal hemorrhage, 483
- Amyloidosis, **213**, 566
  - carpal tunnel syndrome, 426
  - chronic inflammation, 207
  - extraarticular manifestation, 439
  - multiple myeloma, 409
  - serum amyloid A in, 102
- amyloid precursor protein (APP), 490
- Amyotrophic lateral sclerosis (ALS)
  - riluzole for, 518
  - spinal cord lesions, 500
- Anabolic steroids
  - hepatic adenomas and, 375
- Anaerobic metabolism
  - glycolysis, 71
  - pyruvate metabolism, 73
- Anaerobic organisms
  - aspiration and, 175
  - clindamycin, 188
  - Clostridia (with exotoxins), 134
  - culture requirements, **123**
  - glycyclines, 188
  - *Nocardia* vs *Actinomyces*, 135
  - metronidazole, 191
  - overgrowth in vagina, 144
  - pneumonia caused by, 175
- Anal cancer
  - HIV and, 173
  - oncogenic microbes and, 219
- Anal fissures, 351
- Anaphase, 42
- Anaphylaxis, 108
  - blood transfusion, 110
  - complement and, 103
  - epinephrine for, 234
  - IgA-containing products, 112
  - shock with, 299
- Anaplasia, 214
- *Anaplasma* spp
  - anaplasmosis, 145
  - transmission, 142, 144
- Anaplastic thyroid carcinomas, 330
- Anastrozole, 621
  - reproductive hormones and, 620
- Anatomy
  - endocrinal, 312–313
  - gastrointestinal, 345–354
  - hematologic/oncologic, 386–389
  - musculoskeletal, 424–432
  - neurological, 463–485
  - renal, 550
  - reproductive, 591–594
  - respiratory, 628–629
- Anatomy of heart, 264, **271**
- *Ancylostoma* spp
  - diseases associated with, 157
  - infection routes, 154
  - microcytic anemia, 157
  - transmission and treatment, 155
- *Ancylostoma duodenale*, 155
- Androblastomas, 619
- Androgen-binding protein
  - Sertoli cell secretion, 594
- Androgen insensitivity syndrome, **604**
- Androgen-receptor complex
  - pharmacologic control, 620
- Androgen receptor defect, 604
- Androgens, **600**
  - adrenal cortex secretion, 312
  - adrenal steroids and, 318
  - PCOS and, 609
- Androstenedione, 318, 600
  - pharmacologic control, 620
- Anemia, **396**
  - amphotericin B, 195
  - *Ancylostoma*, 157
  - anorexia nervosa, 537
  - azathioprine, 116
  - babesiosis, 153
  - blood oxygen content, 633
  - blood transfusion therapy, 407
  - cephalosporins, 185
  - chloramphenicol, 188
  - cirrhosis, 372
  - cold agglutinin disease, 655
  - colorectal cancer, 371
  - cytarabine and, 417
  - dapsone, 190
  - *Diphyllobothrium latum*, 156
  - as drug reaction, 241
  - epilepsy drugs, 514
  - *Escherichia coli*, 140
  - ESR in, 212
  - extrinsic hemolytic, **401**
  - fibroid tumors, 612
  - G6PD deficiency, 75
  - hepatitis, 200
  - hookworms, 155
  - intrinsic hemolytic, **400**
  - isoniazid, 193
  - kwashiorkor, 67
  - lab values, **402**
  - macrocytic, **398**
  - macro-ovalocytes in, 394
  - malaria, 153
  - microcytic, hypochromic, 396
  - multiple myeloma, 409
  - nonhemolytic, normocytic, **399**
  - nonhomologous end joining, 37
  - normocytic, normochromic, **399**
  - NRTIs, 199
  - penicillin G, V, 185
  - Plummer-Vinson syndrome, 360
  - pregnancy and, 598
  - pure red cell aplasia, 217
  - recombinant cytokines for, 117
  - renal failure, 571
  - ringed sideroblasts in, 395
  - sideroblastic, 63
  - sirolimus, 116
  - spherocytes in, 395
  - sulfa drug allergies as cause, 243
  - thionamides causing, 341
  - trimethroprim, 190
  - tropical sprue, 364
  - vitamin B_9 deficiency, 64
  - vitamin B_{12} deficiency, 65
  - vitamin E deficiency, 66
  - Weil disease, 142
  - Wilson disease, 378
- Anemia of chronic disease, 399
  - hepcidin in, 102
  - rheumatoid arthritis, 439
- Anemic infarcts, 207
- Anencephaly, 461
  - labs/findings, 657
  - polyhydramnios and, 607
- Anergy, **106**
- Anesthetics
  - general principles, **518**
  - inhaled, **519**
  - intravenous, **519**
  - local, **519**
- Aneuploidy, 603
- Aneurysms, **486**
  - atherosclerosis, 292
  - coarctation of aorta, 289
  - Ehlers-Danlos syndrome and, 47
  - MI, 294
  - superior vena cava syndrome, 646
  - vasculitides, 302
- Angelman syndrome
  - chromosome association, 60
  - imprinting, 54
- Angina, 293
  - aortic stenosis, 279
  - atherosclerosis, 292
  - calcium channel blockers for, 304
  - cilostazol/dipyridamole for, 415
  - cocaine causing, 540
  - drug therapy for, **305**
  - glycoprotein IIb/IIa inhibitors for, 415
  - hydralazine causing, 304
  - nitrates for, 305
  - presentation, 652
  - ranolazine for, 305
- Angina pectoris
  - β-blockers for, 237
- Angiodysplasia, 369

Angioedema
  ACE inhibitors, 577
  C1 esterase inhibitor deficiency, 103
  scombroid poisoning, 238
Angiofibromas, 495
Angiogenesis
  bevacizumab and, 420
  in cancer, 215
  wound healing and, 211
Angiokeratomas, 84
Angiomatosis
  von Hippel-Lindau disease, 495, 655
Angiomyolipomas, 495
Angiosarcomas, 375, 450
  carcinogens causing, 219
  nomenclature for, 216
Angiotensin II, 318, 558
  ACE inhibitor effects on, 577
  kidney effects, 559
  nephron physiology, 555
  signaling pathways for, 322
Angiotensin II receptor blockers, **577**
  heart failure, 298
  hypertension, 304
  naming convention for, 244
  preload/afterload effects, 273
Angiotensinogen, 558
Angry patients, 256
Anhedonia, 531
Anhidrosis
  Horner syndrome, 509, 655
  Pancoast tumor, 646
Anidulafungin, 194, 196
Aniline dyes
  transitional cell carcinoma and, 569
Aniridia
  WAGR complex, 569
Anisocytosis, 386
Anitschkow cells, 300
Ankylosing spondylitis, **442**
  HLA-B27 and, 96
  labs/findings, 657
  therapeutic antibodies for, 118
  TNF-α inhibitors for, 457
Annular pancreas, 345
Anopheles mosquito, 153
Anopia
  visual field defects, 511
Anorectal varices
  cirrhosis as cause, 372
  portal circulation, 350
Anorexia nervosa, 537
  anovulation with, 609
  treatment, 661
Anorexia (symptom)
  amphetamines, 540
  hypothalamus and, 466
  renal failure, 571
Anosmia
  zinc deficiency, 67
ANOVA tests, 253
Anovulation
  common causes, **609**
  endometrial hyperplasia, 612
ANP. *See* Atrial natriuretic peptide (ANP)
Antacids, **382**
  metabolic alkalosis with, 561
Anterior cerebral artery, 472
  cavernous sinus, 512
  cingulate herniation, 499
  circle of Willis, 473
  stroke, 484
Anterior chamber (eye), 504
Anterior communicating artery
  circle of Willis, **473**
  saccular aneurysm, 486
Anterior corticospinal tract, 478
Anterior cruciate ligament (ACL) injury
  anterior drawer sign in, 424
  presentation, 652
  "unhappy triad," 425
Anterior drawer sign, 424, 652
Anterior hypothalamus, 466
Anterior inferior cerebellar artery, 473, 484
Anterior perforated substance, 474
Anterior pituitary gland, 313
Anterior spinal artery
  complete occlusion, 500
  stroke, 484
Anterior spinothalamic tract, 478
Anterior superior pancreaticoduodenal artery, 349
Anterior white commissure, 478
Anterograde amnesia, 528
  benzodiazepines, 519
  brain lesions, 481
Anthracosis, 641
  restrictive disease, 639
Anthracyclines, 239
Anthrax, 127, 128, **133**
Anthrax toxin
  Bacillus anthracis and, 133
Antiandrogens, **623**
Antianginal therapy, **305**
Antiapoptotic molecule
  oncogene product, 218
Antiarrhythmic drugs, **308–310**
  torsades de pointes, 239
Anti-β_2 glycoprotein antibodies
  antiphospholipid syndrome, 443
Antibiotics
  acne treatment, 449
  Candida albicans and, 149
  Clostridium difficile with, 652
  Jarlsch-Herxheimer reaction, 143
  long QT interval, 283
  selective growth media, 122
  torsades de pointes, 239
Antibodies
  autoantibodies, **111**
  exo- and endotoxins, 127, 129
  hepatitis viruses, 170
  structure and function, **100**
  therapeutic, **118**
Anticardiolipin
  antiphospholipid syndrome, 443
Anti-centromere antibodies, 657
  scleroderma, 446
Anticholinergic drugs
  Beers criteria, 238
  toxicity treatment for, 239
Anticholinesterase drugs, 232
Anticipation (genetics), 52
Anticoagulant drugs, 391
  acute coronary syndromes, 296
  antiphospholipid syndrome, 443
  atrial fibrillation, 284
  osteoporosis and, 435
  warfarin as, 414
Anticoagulation
  coagulation cascade and, 392
Anticodon loop, 40
Anticonvulsant drugs
  for fibromyalgia, 444
  osteoporosis and, 435
Antidepressant drugs, **544**
  Beers criteria, 238
  for bulimia nervosa, 537
  for fibromyalgia, 444
  long QT interval with, 283
  torsades de pointes, 239
Anti-desmoglein antibodies, 657
Anti-digoxin Fab fragments, 239
  for cardiac glycoside toxicity, 307
Antidiuretic hormone (ADH), **317**, 558
  in diabetes insipidus, 334
  hypothalamus synthesis, 466
  kidney effects, 559
  nephron physiology, 555
  pituitary gland and, 313
  SIADH and, 334
  signaling pathways of, 322
Antidiuretic hormone (ADH) antagonists, 342
Anti-dsDNA antibodies
  lupus, 443
Antiemetic drugs, 383
  long QT interval with, 283
  marijuana as, 541
  torsades de pointes, 239
Anti-endomysial antibodies, 657
Antiepileptic drugs
  cytochrome P-450 and, 243
  rash from, 241
  teratogenicity, 582
Antifungal drugs
  mechanism and use, **194–196**
  tinea versicolor, 148
Antigenic shift/drift, 165
Antigen-presenting cells (APCs)
  B cells as, 388
  CD28, 106
  dendritic cells as, 388
  MHC I and II and, 96
  naive T-cell activation, 99
  in spleen, 94
Antigens
  active immunity, 107
  antibody structure and function, **100**
  blood transfusion reactions, 110
  chronic mucocutaneous candidiasis, 112
  diversity of, 108
  for self, 97
  HLA I and II, **96**
  llymphocyte recognition of, 94
  type and memory, **101**
  vaccination, 107
  variations in, **106**
Anti-gliadin antibodies, 657
Anti-glomerular basement membrane antibodies, 657
Anti-HBc, 170
Anti-HBe, 170
Anti-HBs, 170
Antihelminthic drugs, **196**
  naming convention, 244
Antihistamines
  Beers criteria, 238
  for scombroid poisoning, 238
Antihistone antibodies, 657
  lupus, 443
Antihypertensive drugs
  hypertension in pregnancy, 608
  sexual dysfunction, 537
Anti-IgE monoclonal antibodies, 649
Anti-IgG antibodies, 657
Anti-inflammatory drugs, 455
Antileukotrienes
  for asthma, 649
Antimalarial drugs
  G6PD deficiency, 400
Antimetabolites, **417**
  in cell cycle, 416
Antimicrobial drugs, **183–200**
  naming conventions for, 244
  pregnancy contraindications, **201**
  prophylaxis, **194**
Antimitochrondrial antibodies, 657
Antimuscarinic drugs
  Parkinson disease, 517
  toxicity treatment for, 239
  urgency incontinence, 569
Antimuscarinic reaction, 242
Antimycin A
  electron transport chain, 74
Antimycobacterial drugs, **192**
Antineutrophil cytoplasmic antibodies, 657
Anti-NMDA receptor encephalitis, 217
Antinuclear antibodies (ANA), 657
  lupus, 443
  Sjögren syndrome, 441
Antioxidants
  free radical elimination by, 210
Antiparasitic drugs
  naming convention for, 244
Antiphospholipid syndrome, **443**
Antiphospholipid syndrome autoantibodies, 111
Antiplatelet antibodies, 657
  abciximab as, 118
Antiplatelet drugs
  for acute coronary syndromes, 296
Antiprogestin drugs, **622**
Antiprotozoan drugs, **196**
Antipseudomonal drugs, 183
  cephalosporins, 185
  fluoroquinolones, 191
  penicillins, 184

Antipsychotic drugs, **543**
  antimuscarinic reaction, 242
  dopaminergic pathways, 468
  galactorrhea with, 315
  long QT interval with, 283
  naming convention for, 244
  Parkinson-like syndrome, 242
  PCP overdose, 541
  prolactin and, 316
  tardive dyskinesia, 242
  torsades de pointes, 239
  Tourette syndrome, 527, 542
Anti-Smith antibodies
  lupus, 443
Antisocial personality disorder, 535
  early-onset disorder, 527
Antithrombin
  coagulation cascade and, 392
Antithrombin deficiency, 406
Anti-topoisomerase antibodies, 657
Antitoxins
  as passive immunity, 107
Anti-transglutaminase antibodies, 657
Antitumor antibiotics, **418**
Anti-U1 RNP antibodies, 443
Antiviral therapy, **197**
Anxiety
  benzodiazepine withdrawal, 540
  delirium tremens, 542
  drugs for relief of, 515
  hypercalcemia and, 560
  hyperthyroidism and, 327
  LSD, 541
  MAO inhibitors for, 546
  MDMA withdrawal, 541
  neurotransmitters, 465
  nicotine withdrawal, 540
Anxiety disorder, **532**
  atypical antipsychotics for, 543
Aorta
  aneurysm of, 292
  coarctation of, **289**, 290
  congenital heart disease, 288
  diaphragm, 629
  dissection in, 293
  ECG and, 282
  embryonic development, 268–269
  fetal circulation, 270
  gastrointestinal blood supply, **348**
  horseshoe kidney and, 549
  retroperitoneal, 345
  in syphilitic heart disease, 300
  traumatic rupture of, 292
  “tree bark” appearance of, 300
Aortic aneurysm, **292**
  associations, 664
  Ehlers-Danlos syndrome, 47
  hypertension, 290
  Marfan syndrome, 290
  syphilitic heart disease, 300
Aortic arch derivatives, **586**
Aortic, coarctation
  labs/findings, 660
Aortic dissection, **293**
  associations with, 664
  hypertension, 290
  Marfan syndrome, 652
  Marfan syndrome as cause, 290
Aortic insufficiency
  syphilitic heart disease, 300
Aorticopulmonary septum, 269
  embryologic derivatives, 581
Aortic regurgitation
  diastolic murmur in, 278
  heart murmurs with, 279
  Marfan syndrome, 290
  presentation, 652
  pulse pressure in, 272
Aortic root dilation
  heart murmur with, 279
aortic stenosis
  presentation, 656
Aortic stenosis
  ejection click and, 665
  heart murmurs, 279
  macroangiopathic anemia, 401
  paradoxical splitting in, 277
  presentation, 656
  pulse pressure in, 272
  S4 heart sound and, 668
  systolic murmur in, 278
  Williams syndrome, 290
Aortic valve
  cardiac cycle, 276
  embryological development, 268
  sclerosis, 278
Aortitis
  syphilis, 143, 180
APC gene, 218
  adenomatous colonic polyps and, 370
  colorectal cancer and, 372
  familial adenomatous polyposis and, 370
“Ape hand” (median nerve injury), 427, 429
Apgar score, **599**
Aphasia, **486**
  dementia and, 529
  MCA stroke, 484
Aphthous stomatitis
  Crohn disease, 365
Apixaban
  as anticoagulant, 391
  factor Xa inhibitors, **415**
Aplasia cutis
  methimazole, 341
Aplasia cutis congenita
  fetal methimazole exposure, 582
Aplastic anemia, 399
  in anemia taxonomy, 396
  chloramphenicol, 188
  as drug reaction, 241
  Fanconi anemia, 656
  neutropenia with, 402
  thionamides, 341
Aplastic crisis
  hereditary spherocytosis, 400
  sickle cell anemia, 400
Apolipoproteins, **89**
Aponeurosis of external oblique muscle, 354
Apoptosis, **204**
  corticosteroids, 402
  evasion in cancer, 215
  malignant tumors, 216
Appendages (appendages), 120
Appendicitis, **366**
  mittelschmerz vs, 596
Appetite regulation, **317**
“Apple core” lesion (X-ray), 371, 657
Apraxia
  dementia and, 529
Aprepitant, 383
Aquaporin
  renin-angiotensin-aldosterone system, 558
Aqueous humor pathway, **505**
Arabinoglycan synthesis, 192
Arabinosyltransferase, 193
Arachidonic acid pathway, **455**
Arachnodactyly
  Marfan syndrome, 652
Arachnoid
  CSF absorption, 473, 492
  meninges, 465
  meningioma, 496
  ventricular system, 474
Arcuate artery, 550
Arcuate fasciculus
  aphasia and, 486
  diagram, 471
Area postrema, 466
Arenaviruses
  characteristics of, 163, 164
Arginine
  classification, 77
  cystinuria, 81
  derivatives of, 79
  histones, 32
  kidney stones and, 567
Arginosuccinate
  urea cycle, 78
Argyll Robertson pupils
  presentation, 655
  syphilis, 143, 180
  tabes dorsalis, 500
Arhythmia
  atiral fibrillation, 665
Aripiprazole, 543
Arm abduction, **425**
Armadillos (disease vectors), 144
Aromatase, 600
Aromatase inhibitors, **621**
  breast cancer, 661
Aromatic amines
  as carcinogens, 219
Arrhythmia
  amphotericin B, 195
  amyloidosis and, 213
  associations of, 665
  diabetic ketoacidosis, 337
  diptheria, 135
  hyperthyroidism, 327
  hypokalemia and, 560
  local anesthetics causing, 519
  macrolides, 189
  McArdle disease, 83
  MI, 294
  muscular dystrophy, 57
  shock caused by, 299
  sleep apnea and, 642
  stimulants and, 540
  thyroid hormones and, 342
  treatment, 661
Arsenic
  angiosarcomas, 375, 450
  as carcinogen, 219
  glycolysis and, 71
  inhalational injury, 640
  toxicity symptoms, 72
  toxicity treatment for, 239
Artemether, 196
Arterial oxygen saturation, 633
Arterial PCO$_2$, 630, 634
Arteries, anatomy of, 271
Arteriolosclerosis, 336
Arteriosclerosis, **291**
  pulmonary hypertension, 643
Arteriovenous malformations (AVMs), 303
Arteritis
  headaches, 488
Artesunate
  malaria, 153, 196
Arthralgias
  alkaptonuria, 80
  cocciciomycosis, 147
  Henoch-Schönlein purpura, 303
  hepatitis viruses, 168
  rubella, 165
  serum sickness, 109
  vitamin A toxicity, 62
Arthritis, **439**
  AA amyloidosis and, 213
  autoantibodies, 111
  azathioprine for, 417
  Campylobacter jejuni, 140
  carpal tunnel syndrome and, 426
  celecoxib for, 456
  chlamydiae, 146, 180
  Crohn disease, 365
  gonorrhea, 138, 176, 180
  immunosuppressants, 116
  inflammatory bowel disease, 96
  LMN facial nerve palsy, 656
  lupus, 443
  Lyme disease, 142
  Paget disease of bone, 652
  parvovirus, 160
  reactive arthritis, 442
  septic, 441
  Sjögren syndrome, 653
  Staphylococcus aureus, 131
  Takayasu arteritis, 302
  therapeutic antibodies, 118
  ulcerative colitis, 365
  Whipple disease, 656
Arthropathy
  hemochromatosis, 378
Arthus reaction, 109
Arylcyclohexylamines
  intravenous anesthetics, 519
Arylsulfatase A
  metachromatic leukodystrophy, 84
Asbestos
  carcinogenicity, 219
  lung cancer and, 647

Asbestosis
  characteristics, 641
  restrictive disease, 639
Ascaris spp, 154
Ascaris lumbricoides, 155
Ascending aorta
  embryological development of, 268
Ascending cholangitis, 379
Ascending colon, 345
Aschoff bodies, 300
Ascites
  Budd-Chiari syndrome, 375, 652
  cirrhosis, 372
  hepatocellular carcinoma, 375
  Meigs syndrome, 610
  spontaneous bacterial peritonitis, 373
Asenapine, 543
Aseptic meningitis
  mumps, 166
  picornaviruses, 163
Asherman syndrome, 622
Ashkenazi Jews
  disease incidence, 84
Ash-leaf spots, 495
Aspartame, 80
Aspartate
  urea cycle, 78
Aspartate aminotransferase (AST), 373
  hepatitis, 168
  toxic shock syndrome, 131
Aspartic acid, 77
Aspart insulin, 340. *See also* Insulin
Aspergillosis
  Aspergillus fumigatus, 149
  bronchiectasis, 639
  echinocandins, 196
Aspergillus spp
  as catalase-positive organism, 124
  chronic granulomatous disease, 105
  immunodeficiency infections, **114**
Aspergillus fumigatus, **149**
  HIV-positive adults, 173
Aspiration
  ARDS and, 642
  in utero "breathing," 626
  lung abscess, 646
  $\dot{V}/\dot{Q}$ mismatch, 634
Aspiration pneumonia
  alcoholics, 175
  clindamycin, 188
  Klebsiella, 140
  nosocomial infections, 181
Aspirin, **456**
  acute coronary syndromes, 296
  arachidonic acid pathway and, 455
  cyclooxygenase, 393
  hemolysis in G6PD deficiency, 241
  for ischemic stroke, 482
  Kawasaki disease, 302, 662
  polycythemia vera, 411
  Reye syndrome and, 373
  uncoupling agent, 74
  as weak acid, 226
  zero-order elimination of, 226
Asplenia
  Howell-Jolly bodies, 395
  target cells, 395
Asterixis, 489
  cirrhosis, 372
  hepatic encephalopathy, 374
  hyperammonemia, 78
  renal failure, 571
Asthma, **638**
  albuterol for, 234
  β-blockers and, 237
  breast milk and, 599
  cholinomimetic agents and, 232
  cromolyn sodium for, 387
  drug therapy, **649**
  eczema and, 449
  eosinophilia and, 387
  epinephrine for, 234
  gastroesophageal reflux disease, 360
  immunosuppressants, **116**
  muscarinic antagonists for, 233
  omalizumab for, 118
  pulsus paradoxus in, 300
  salmeterol for, 234
  type I hypersensitivity, 108
Astigmatism, 504
Astrocytes, **463**
  foot processes, 466
  origin of, 460
Astrocytomas, 664
  GFAP stain for, 44
Ataxia
  abetalipoproteinemia, 89
  amantadine toxicity, 517
  Angelman syndrome, 54
  ataxia-telangiectasia, 37
  cerebellar hemisphere lesions, 481
  cerebellar vermis lesions, 481
  epilepsy drugs, 514
  Friedreich, 501
  hypnotics, 515
  metachromatic leukodystrophy, 84, 494
  normal pressure hydrocephalus, 492
  opsoclonus-myoclonus syndrome, 217
  peroxisome disease, 43
  prion disease, 174
  psychoactive drug intoxication, 540
  Rett syndrome, 527
  streptomycin, 193
  syphillis, 143
  tabes dorsalis, 500
  trinucleotide repeat expansion disease, 58, 60
  vitamin B_{12} deficiency, 500
  Wernicke-Korsakoff syndrome, 62, 481, 541
Ataxia-telangiectasia, 37, 113
Atazanavin, 199
Atazanavir, 197
Atelectasis
  intrapleural pressures, 631
  physical findings with, 643
Atenolol, 237, 309
Ateriolosclerosis, 291
Atherosclerosis, **292**
  abdominal aortic aneurysms and, 292
  aortic aneurysms, 664
  diabetes mellitus and, 336
  familial dyslipidemias, 90
  homocystinuria as cause, 80
  sites of, 668
  stable angina with, 293
  transplant rejection, 115
Athetosis, 481, 489
ATM gene, 113
Atomoxetine, 527, 661
Atonic seizures, 487
Atopic dermatitis, 449
Atopic reactions, 108
Atorvastatin, 306
Atovaquone
  babesiosis, 153
  malaria, 153
  P. falciparum, 196
  for *Pneumocystis jirovecii*, 150
ATPase, 378
Atracurium, 520
Atria
  cardiac tumors, 301
  embryological development of, 268–269
Atrial amyloidosis, 213
Atrial fibrillation
  β-blockers for, 309
  calcium channel blockers for, 310
  cardiac glycosides for, 307
  ECG tracing of, 284
  embolic risk with, 665
  embolic stroke, 482
  hypertension as cause, 290
  jugular venous pulse in, 276
  potassium channel blockers for, 309
  sleep apnea, 642
Atrial flutter
  β-blockers for, 309
  ECG tracing of, 284
  potassium channel blockers for, 309
Atrial natriuretic peptide (ANP), **285**, 558
  amyloidosis and, 213
  kidney effects, 559
  in SIADH, 334
  signaling pathways for, 322
Atrial septa
  embryological development of, 268
Atrial septal defect (ASD), 289
  congenital rubella, 290
  diastolic murmur in, 278
  Down syndrome, 290
  fetal alcohol syndrome, 290
Atrioventricular block
  β-blockers as cause, 237
  β-blockers in, 309
  calcium channel blockers, 304, 310
  ECG tracings, 284
  Lyme disease, 142
Atrioventricular canals, 269
Atrioventricular node
  conduction pathway, 282
  ECG and, 282
Atrioventricular septal defect (AVSD), 59
Atrioventricular valves
  embryological development of, 268
Atrophic gastritis
  associations with, 665
  gastrin in, 356
Atrophy, 214
  amyotrophic lateral sclerosis, 500
  cerebral, 483
  motor neuron signs, 499, 501
  neurodegenerative disorders, 490
  optic disc/nerve, 494, 506
  ventriculomegaly, 492
Atropine, **233**
  antimuscarinic reaction, 242
  for β-blocker overdose, 309
  cholinesterase inhibitor poisoning, 232
  toxicity treatment, 239
Attention deficit disorder (ADD)
  amphetamines for, 234
Attention-deficit hyperactivity disorder (ADHD), 527
  drug therapy for, 542
  smoking and, 582
  sympatholytic drugs for, 235
  Tourette syndrome, 527
  treatment, 661
Attributable risk (AR), 248, 669
Atypical antidepressants, **546**
Atypical antipsychotic drugs, **543**
  bipolar disorder, 531, 661
  postpartum psychosis, 532
  schizophrenia, 530
Atypical depression, 546
Atypical lymphocytes, 657
Atypical pneumonias
  chlamydiae, 146
  macrolides, 189
  typical organisms, 645
Auditory cortex
  diagram, 471
  thalamic relay, 468
Auditory hallucinations, 529, 530
Auditory physiology, **503**
Auer rods, 657
  in AML, 410
Auramine-rhodamine stain, 122
Auscultation of heart, **278**
Auspitz sign, 449
Autism spectrum disorder, 527
  double Y males and, 603
  fragile X syndrome, 58
Autoantibodies, **111**
Autoclaves
  disinfection/sterilization, 200
  spore-forming bacteria, 127
Autografts, 114
Autoimmune anemia, 396
Autoimmune diseases
  acute pericarditis, 300
  collagen and, 46
  preeclampsia and, 608
  self-antigen in, 97
Autoimmune gastritis, 362
Autoimmune hemolytic anemia, 108, 401
  cephalosporins, 185

Autoimmune hepatitis, 111
Autoimmune hypothyroidism, 169
Autoimmune lymphoproliferative syndrome, 204
Autoimmune membranous nephropathy, 111
Autoimmune regulator (AIRE), 97
Autonomic drugs, 229–238
  naming conventions for, 244
Autonomic insufficiency, 234
Autonomy (ethics), 253
Autoregulation of blood flow, **286**
Autosomal dominant disorders
  Brugada syndrome, 285
  hyper-IgE syndrome, 112
Autosomal dominant hyper-IgE syndrome
  presentation, 655
Autosomal dominant inheritance
  diseases, 56
  mode of, 55
Autosomal dominant polycystic kidney disease (ADPKD), 573
  chromosome association, 60
  saccular aneurysms and, 486
Autosomal recessive disorders
  adenosine deaminase deficiency, 113
  Chédiak-Higashi syndrome, 113
  IL-12 receptor deficiency, 112
  leukocyte adhesion deficiency, 113
  severe combined immunodeficiency, 113
  Wilson disease, 378
Autosomal recessive inheritance
  diseases, 56
  mode of, 55
Autosomal recessive polycystic kidney disease (ARPKD), 573
  Potter sequence caused by, 548
Autosomal trisomies, **59**
  karyotyping for, 51
Autosplenectomy
  associations with, 664
  sickle cell anemia, 400
Avascular necrosis, **436**
  scaphoid bone, 426
  sickle cell anemia, 400
Avoidant personality disorder, 535
Axillary lymph nodes, 93
  breast cancer and, 616
Axillary nerve, 427
Axonal injury, 465
Axonemal dynein, 45
Azathioprine
  allopurinol and, 457
  antimetabolites, 417
  in cell cycle, 416
  for Crohn disease, 365
  immunosuppressant, 116
  pancreatitis caused by, 240
  targets of, 117
Azithromycin, 138
  babesiosis, 153
  chlamydiae, 146
  gonococci, 138
  prophylaxis in HIV, 194
  macrolides, 189
  mechanism (diagram), 183
  Mycobacterium avium-intracellulare, 136, 192
Azoles, **195**
  mechanism (diagram), 194
  opportunistic fungal infections, 149
  vaginal infections, 177
Azotemia
  acute interstitial nephritis, 572
  nephritic syndrome and, 564
Aztreonam, 183, 186

B
B7 protein
  naive T-cell activation, 99
B19 virus, 160
Babesia spp, 142, **153**
  anemia, 401
Babesiosis, 153
Babinski reflex, 258
  motor neuron signs, 499
  primitive reflexs, 480
Bachmann bundle, 282
Bacillary angiomatosis, 450
  animal transmission, 144
  HIV-positive adults, 173
Bacilli, 121
  Gram stain identification of, 130
Bacillus spp
  Gram-positive algorithm, 130
  taxonomy, 121
Bacillus anthracis, **133**
  capsule composition, 120
  exotoxin production, 128
  spore formation, 127
Bacillus cereus, **134**
  food poisoning, 174, 665
  spore formation, 127
Bacitracin
  Gram-positive antibiotic test, 130
  mechanism (diagram), 183
  sensitivity to, 130, 132
Bacitracin response, 657
Back pain
  G6PD deficiency and, 400
Baclofen
  mechanism and use, **520**
  multiple sclerosis, 493
Bacteremia
  brain abscesses, 176
  cutaneous anthrax, 133
  daptomycin, 191
  Staphylococcus gallolyticus, 133
  Streptococcus bovis, 133
  tuberculosis, 136
Bacteria
  biofilm-producing, 125
  encapsulated, 124
  genetics, 126, 127
  hemolytic, 131
  highly resistant, **194**
  normal flora, 174
  pigment-producing, 125
  special culture requirements, **123**
  special populations, 182
  spore-forming, **127**
  stains for, 122
  structures of, **120**
  taxonomy, 121
  virulence factors, 124, 125
  zoonotic, 144
Bacterial capsules, 120
Bacterial endocarditis, **299**
  daptomycin, 191
  presentation, 656
  Staphylococcus aureus, 131
  Streptococcus sanguinis, 132
Bacterial meningitis, 664
Bacterial peritonitis (spontaneous), 373
Bacterial toxins
  effects of, **106**
  neutralization of, 101
Bacterial vaginosis
  characteristics of, 154, 177
  Gardnerella vaginalis, 144
Bacteroides spp
  alcoholism, 175
  anaerobic organism, 123
  clindamycin, 188
  lung abscesses, 646
  metronidazole, 191
  nosocomial infections, 181
  taxonomy, 121
Bacteroides fragilis, 174
"Bag of worms," 618
Baker cyst, 425
  tibial nerve injury, 430
BAK protein, 204
Balancing (quality measurement), 261
"Bamboo spine" (X-ray), 442, 657
Band cells, 386
Barbiturates
  intoxication and withdrawal, 540
  intravenous anesthetics, 519
  mechanism and use, **515**
  naming convention for, 244
  sleep alterations, 467
Baroreceptors, **285**
Barr bodies, 32
Barrett esophagus, **361**
  metaplasia and, 214
Bartonella spp
  animal transmission, 144
  endocarditis, 299
  taxonomy, 121
Bartonella henselae
  bacillary angiomatosis, 450
  granulomatous diseases, 211
  HIV-positive adults, 173
Bartonella quintana, 157
Bartter syndrome, **556**
  markers in, 560
Basal cell carcinomas, **454**
  5-fluorouracil for, 417
  sunburn and, 453
Basal ganglia, **470**
  intraparenchymal hemorrhage, 483
  lesions in, 481
  microaneurysms, 486
  movement disorders, **489**
  thalamic connections, 468
Basal lamina, 46
Basal metabolic rate, 321
Basal plate, 460
Base excision repair, **37**
Basement membrane
  Alport syndrome and, 565
  autoantibodies to, 111
  barrel hoop, 94
  blood-brain barrier, 466
  collagen in, 46
  filtration, 553
  glomerular filtration barrier, 551
  in glomerulus, 550
Basic amino acids, 77
Basilar artery
  circle of Willis, 473
  herniation syndromes, 499
  stroke efects, 485
Basilar membrane (cochlea), 503
Basiliximab
  immunosuppressant, 116
  targets of, 117
Basophilia, 387
Basophilic stippling, 394, 657
  lead poisoning, 397
  sideroblastic anemia, 397
Basophils, **387**
  CML, 410
  hypersensitivity reaction, 108
  IgE antibody, 101
BAX protein, 204
B-cell lymphomas, 668
  HIV-positive adults, 173
  oncogenes and, 218
B cells, **388**
  activation, **99**, 101
  adaptive immunity, 95
  anergy, 106
  cell surface proteins, 106
  class switching, 99
  cytokines and, 104
  disorders of, 112, 113
  functions of, 97, 388
  glucocorticoid effects, 116
  immunodeficiency infections, **114**
  in lymph node, 92
  neoplasms, 408
  non-Hodgkin lymphoma, 407
  sirolimus effect, 116
  spleen, 94
BCG vaccination, 136
BCG vaccine
  IL-12 receptor deficiency and, 112
  live attenuated, 107
BCL-2 gene, 218
Bcl-2 protein, 204
BCR-ABL gene, 218
Becker muscular dystrophy, **57**
  presentation, 656
Beck triad of cardiac tamponade, 300, 654
Beckwith-Wiedemann, 569
Bedwetting. *See* Nocturnal enuresis
Beers criteria, **238**
Bell palsy, 502
  Lyme disease, 142, 182
  sarcoidosis and, 444

- Bell-shaped distribution, 251
- Bence Jones protein, 409
- Bendazoles, 155
- “the bends,” 436
- Beneficence (ethics), 253
- Benign breast disease, **615**
- Benign prostatic hyperplasia (BPH), **619**, 667
  - α-blockers for, 236
  - hydronephrosis and, 568
  - postrenal azotemia, 571
  - tamsulosin for, 623
  - treatment, 661
- Benign tumors, 216
- Benzathine pencillin G, 194
- Benzene
  - aplastic anemia, 241, 399
  - myelodysplastic syndromes, 409
- Benzidine as carcinogen, 219
- Benznidazole, 154
- Benzoate, 78
- Benzocaine, 519
  - methemoglobinemia, 632
- Benzodiazepines, **515**
  - addictive risk, 515
  - alcohol withdrawal, 542, 661
  - anaesthetic adjuncts, 519
  - Beers criteria, 238
  - cocaine overdose, 540
  - epilepsy, 514
  - generalized anxiety disorder, 533
  - intoxication and withdrawal, 540
  - naming convention for, 244
  - panic disorder, 533
  - PCP overdose, 541
  - phobias, 533
  - sleep, effect on, 467
  - toxicity treatment for, 239
- Benzoyl peroxide for acne, 449
- Benztropine, 233, 517
- Beriberi
  - cardiomyopathy, 297
  - vitamin B_1 deficiency, 62
- Berkson bias, 250
- Bernard-Soulier syndrome, 393, 405, 664
- Berylliosis, **641**
  - granulomatous disease, 211
- β_1-blockade, 273
- β_2-agonists
  - asthma, 649
  - insulin and, 314
  - naming convention for, 244
- β_2-microglobulin
  - MHC I and II and, 96
- β-amyloid protein (Alzheimer disease), 213
- β-blockers, **237**
  - acute coronary syndromes, 296
  - angina, 305
  - antiarrhythmic drugs, **309**
  - aortic dissections, 293
  - for cocaine overdose, 234, 540
  - diabetes and, 237
  - dilated cardiomyopathy, 297
  - essential tremor, 489
  - glaucoma, 521
  - heart failure, 298
  - hydralazine and, 304
  - hyperkalemia, 560
  - hypertension, 304
  - hypertrophic cardiomyopathy, 297
  - juxtaglomerular apparatus effects, 558
  - migraine headaches, 488
  - naming convention for, 244
  - overdose treatment, 309
  - for pheochromocytomas, 326
  - phobias, 533
  - for thyroid storm, 329
  - toxicity treatment for, 239
- β cells, 313
  - diabetes mellitus type 1 and 2, 337
  - insulinomas of, 338
  - insulin secretion by, 314
- β-dystroglycan, 57
- β-galactosidase, 138
- β-glucan, 196
- β-glucoronidase, 386
- β-hCG
  - autosomal trisomies, 59
  - as tumor marker, 220
- β-hemolysis, 129
- β-hemolytic bacteria, 131
- β-hydroxybutyrate, 86
- β-interferon
  - multiple sclerosis, 493
- β-lactam antibiotics, 183
- β-lactamase inhibitors, **184**
- β-lactams, 452
- Betamethasone, 455
- β-thalassemia, 397
  - allelic heterogeneity, 53
  - chromosome association, 60
  - intron/exon splicing variants, 39
- Betaxolol, 237
  - glaucoma, 521
- Bethanechol, 232
- Bevacizumab, 118, **420**
- Bezafibrate, 306
- Bias and study errors, **250**
- Bicarbonate
  - carbon dioxide transport, 635
  - drug overdoses, 226
  - GI secretion, 357
  - pancreatic insufficiency, 364
  - salicylate toxicity, 239
  - TCA toxicity, 239
- Biceps brachii muscle
  - Erb palsy, 428
- Biceps tendon, 425
- Bicornuate uterus, 590
- Bicuspid aortic valve
  - aortic dissection and, 293
  - coarctation of aorta and, 289
  - heart murmur with, 279
  - thoracic aortic aneurysms and, 292
  - Turner syndrome, 290, 603
- Bifurcation external landmarks, 629
- Biguanide drugs, 340
- Bilaminar disc, 580
- Bilateral acoustic schwannomas, 652
- Bilateral adenopathy, 444
- Bilateral renal agenesis
  - oligohydramnios and, 607
  - Potter sequence, 548
  - pulmonary hypoplasia and, 626
- Bile, **358**
  - hereditary hyperbilirubinemias, 377
  - secretin effect on, 356
- Bile acid resins, 306
- Bile acids
  - lipid transport, 88
  - reabsorption of, 306
- Bile canaliculus, 352
- Bile duct, 353
- Bile ductule, 352
- Bile salts, 358
  - in cholelithiasis, 379
- Biliary cirrhosis, 372, 376
  - cystic fibrosis, 56
  - labs/findings, 657
- Biliary colic, 379
- Biliary structures, **353**
- Biliary tract disease, **378**
  - *Clonorchis sinensis*, 157
- Biliary tract infections
  - Enterococci, 133
- Bilious vomiting, 367
- Bilirubin, **359**
  - bile, 358
  - cholelithiasis, 379
  - hereditary hyperbilirubinemias, 377
  - liver marker, 373
  - toxic shock syndrome, 131
- Bimatoprost, 521
- Bimodal distribution, 251
- Binge eating disorder, 537
- Bioavailability, 225
- Biochemistry, **32–89**
  - cellular, 42–48
  - genetics, 52–61
  - laboratory techniques, 48–52
  - metabolism, 68–90
  - molecular, 32–41
  - nutrition, 61–68
- Biofilm-producing bacteria, 125
- Biostatistics/epidemiology, **246–252**
- Bipolar disorder, 530, **531**
  - drug therapy for, 542, 543
  - lithium for, 544
  - postpartum psychosis, 532
  - treatment, 661
- Birbeck granules, 660
  - Langerhans cell histiocytosis, 412
- “Bird’s beak” sign (X-ray), 360
- Birds (disease vectors), 144, 146
- Bismuth, **382**
- Bisphosphonates, **456**
  - esophagitis with, 240
  - naming convention for, 244
  - for osteoporosis, 435
- Bitemporal hemianopia, 511
  - craniopharyngioma, 498
  - hypopituitarism as cause, 335
  - Nelson syndrome as cause, 332
  - optic chiasm compression, 486
  - pituitary adenoma, 496
  - visual field defects, 511
- Bitot spots, 62
- Bivalirudin, 413
- BK virus, 160
- Black eschar, 133
- Blackflies (disease vectors), 155
- Black liver, 665
- Black lung disease, 641
- Bladder, 592
  - bethanechol effect on, 232
  - BPH and, 619
  - Brenner tumor, 610
  - development of, 585
  - estrophy, 591
  - female anatomyh, 606
  - lymphatic drainage, 591
  - placenta percreta, 606
  - spasm treatment, 233
  - transitional cell carcinoma, 569
  - urachus, 585
- Bladder cancer
  - cisplatin/carboplatin for, 419
  - hematuria, with, 562
  - hypercalcemia and, 217
  - oncogenic microbes and, 219
  - *Schistosoma haematobium*, 156, 157
- Blast crisis in CML, 665
- Blastocyst implantation, 580
- *Blastomyces* spp
  - amphotericin B, 195
  - itraconazole, 195
- Blastomycosis, **147**
- Bleeding
  - adenomatous polyps, 370
  - control of, 346
  - direct factor Xa inhibitors, 415
  - direct thrombin inhibitors, 413
  - diverticulosis, 366
  - essential thrombocythemia, 411
  - glycoprotein IIb/IIa inhibitors, 415
  - heparin, 413
  - inflammatory bowel disease, 365
  - peptic ulcer disease, 363
  - thrombolytics, 415
  - variceal, 356
  - warfarin, 414
- Bleomycin, 418
  - in cell cycle, 416
  - pulmonary fibrosis, 242
  - targets of, 416
- Bleomycin toxicity, 422, 639
- Blepharospasm
  - dystonia, 489
- Blindness
  - *Chlamydia trachomatis*, 146
  - conversion disorder, 536
  - giant cell arteritis, 302
  - neonatal, 138
  - *Onchocerca volvulus*, 155
  - temporal arteritis, 668
  - *Toxocara canis*, 155
- Blistering skin disorders, **452**
- Blood
  - chocolate-colored, 632
  - coagulation and kinin pathways, 391
  - embryologic derivatives, 581

Blood *(continued)*
  hCG detection in, 598
  metrorrhagia, 597
  oxygen content, **633**
  in placenta, 584
  umbilical cord, 585
  urethral injury, 593
  viscosity of, 634
Blood-brain barrier
  anesthetics, 518
  astrocytes, 463
  function and mechanism, **466**
  L-DOPA, 518
Blood flow exercise response, 635
Blood groups, **390**
Blood pH
  diuretic effects on, 576
Blood pressure
  α-blocker effect on, 236
  angiotensin II effects, 558, 559
  antianginal therapy, 305
  antidiuretic hormone regulation of, 317
  cortisol effect on, 319
  fenoldopam and, 304
  renal disorders and, 560
  renin-angiotensin-aldosterone system, 558
  sympathomimetic effect on, 235
Blood-testis barrier, 466
Blood transfusions, **407**
  reactions, **110**
Blood vessels
  collagen in, 46
  Ehlers-Danlos syndrome, 46
  hereditary hemorrhagic telangiectasia, 303
Bloody diarrhea, **175**
  amebiasis, 151
  Campylobacter jejuni, 140, 144
  Shigella, 141
  ulcerative colitis, 365
Bloody stool, 351
Blotting procedures, **49**
Blown pupils, 511
  CN III damage, 511
  herniation syndromes, 499
  saccular aneurysms, 486
"Blue babies," 288
Blueberry muffin rash
  cytomegalovirus, 178
  rubella, 165, 178
  Toxoplasma gondii, 178
"Blue kids," 289
Blue sclerae, 47
  osteogenesis imperfecta, 652
BNP. *See* Brain natriuretic peptide (BNP)
Body dysmorphic disorder, 533
Boerhaave syndrome, 360
Bombesin, 325
Bone cancer, 437
  primary bone tumors, **438**
Bone crises, 84
Bone disorder lab values, **437**
Bone disorders
  "brown" tumor, 657
  osteogenesis imperfecta, **47**
  pain, 652
  raised periosteum, 660
  "soap bubble" (x-ray), 660
Bone formation, **434**
Bone fractures
  child abuse sign, 526
  fat embol from, 637
Bone lesions
  adult T-cell lymphoma, 408
  Langerhans cell histiocytosis, 412
  multiple myeloma, 409
Bone marrow suppression, 195
Bone marrow transplant
  osteopetrosis, 435
  severe combined immunodeficiency, 113
Bones
  collagen in, 46
  cortisol effect on, 319
  lytic/blastic metastases, 221
  PTH effect on, 320
  renal osteodystrophy, 571
  T_3 hormone and, 321
Bone tumors, **438**
"Boot-shaped" heart (X-ray), 657
Borderline personality disorder, 535
  dissociative identity disorder, 528
Bordetella spp, 121
Bordetella pertussis, **139**
  culture requirements, 123
  exotoxin production, 128
  Gram-negative algorithm, 137
  macrolides, 189
  vaccines, 139
Bordet-Gengou agar, 123
Borrelia spp, **142**
  Giemsa stain, 122
  taxonomy, 121
Borrelia burgdorferi
  animal transmission, 144
  coinfection with, 153
  facial nerve palsy, 182
  Lyme disease, **142**
  tetracyclines, 188
Borrelia recurrentis
  animal transmission, 144
  antigenic variation, 106
  vectors, 157
Bortezomib, 420
Bosentan, 648
Botulinum, 231
Botulinum toxin
  lysogenic transduction, 126
  passive antibodies for, 107
  toxin effects, 128
Botulism
  Clostridium botulinum, 134
  exotoxin, 127
Bovine spongiform encephalopathy (BSE), 174
Bowel smooth muscle activation, 232
Bowel stenosis, 366
Bowen disease, 617
Bowenoid papulosis, 617
Bowman capsule, 553
Brachial artery, 432
Brachial plexus lesions, **428**
Brachiocephalic artery, 473
Bradycardia
  amiodarone and, 309
  atropine for, 233
  β-blockers and, 237, 309
  cholinesterase inhibitor poisoning, 232
  dopamine for, 234
  on ECG, 282
  hypermagnesemia, 560
  hypothyroidism, 327
  RCA infarct, 271
  reflex, 558
  sympatholytic drugs and, 235
Bradykinin
  ACE inhibitors and, 577
  breakdown of, 558
  C1 esterase inhibitor deficiency, 103
Bradykinin, 577
BRAF gene, 218
  melanomas and, 454
  papillary thyroid carcinoma and, 330
  vemurafenib and, 421
Brain
  blood flow autoregulation, 286
  choriocarcinoma and, 618
  embryologic derivatives, 581
  embryology of, 460
  glucose usage by, 314
  ischemia in, 206
  metastasis to, 221
  ring-enhancing lesions, 660
  T_3 hormone and, 321
Brain abscesses
  HIV-positive adults, 176
  Toxoplasma gondii, 152, 173
Brain cysts, 157
Brain infarcts, 205
Brain injury
  gastritis with, 362
  hypopituitarism from, 335
Brain lesions, **481**
Brain natriuretic peptide (BNP), **285**, 558
  in SIADH, 334
  signaling pathways for, 322
Brain stem
  dorsal view, **475**
  ventral view, **474**
Brain tumors
  adult primary, **496–497**
  associations with, 664
  biopsy findings, 660
  childhood primary, 498
  metastatic source, 221
  nitrosureas for, 418
Branched-chain ketoacid dehydrogenase, 62
Branchial apparatus, **586**
Branchial arch derivatives, **587**
Branchial cleft derivatives, **586**
Branchial pouch derivatives, **588**
Branching enzyme (glycogen metabolism), 82
Branching filamentous bacteria
  Gram stain identification, 130
  taxonomy, 121
Branching gram-positive rods/sulfur granules, 657
BRCA1/BRCA2 genes, 218
  breast cancer and, 616
  ovarian neoplasms, 610
Breast cancer, **616–617**
  aromatase inhibitors for, 621
  breastfeeding and, 599
  hormonal contraception contraindication, 622
  hypercalcemia and, 217
  incidence/mortality of, 216
  key associations, 664
  oncogenes and, 218
  paclitaxel for, 419
  paraneoplastic cerebellar degeneration and, 217
  postmenopausal women, 661
  tamoxifen for, 421
  trastuzumab for, 421
  tumor suppressor genes and, 218
Breast disorders
  benign, **615**
  malignant, **616**
Breastfeeding, 599
  ovarian neoplasms and, 610
Breast milk. *See also* Lactation
  IgA antibodies in, 101
  prolactin and, 316
Breast/ovarian cancer
  incomplete penetrance, 52
Breast/ovarian cancers
  BRCA1 mutation, 37
Breast pathology, **614**
Breast trauma, necrosis caused by, 205
Brenner tumors, 610
Bretylium, 231
Brief psychotic disorder, 530
Brimonidine, 521
Brittle hair, 47
Broad-base budding, 147
Broad ligament, 592
Broca area
  aphasia, 486
  diagram, 471
  MCA stroke, 484
Bromocriptine, 517. *See also* Dopamine agonists
  prolactin and, 316
Bronchi, 628
Bronchial carcinoid tumors, 647
Bronchiectasis
  Aspergillus fumigatus, 149
  cystic fibrosis, 56
  Kartagener syndrome, 45, 656
Bronchioalveolar cell carcinomas, 647
Bronchioles, 628
  histamine receptors and, 230
Bronchiolitis obliterans, 115
Bronchiolitis obliterans organizing pneumonia (BOOP), 645
Bronchitis
  croup, 166
  cystic fibrosis, 56
  Haemophilus influenzae, 138

Bronchoconstriction, 649
Bronchodilation, 649
  sympathetic receptors and, 230
Bronchogenic apical lung tumor, 657
Bronchogenic carcinomas
  asbestosis and, 641
  carcinogens causing, 219
Bronchogenic cysts, 626
Bronchopneumonia, 645
Bronchopulmonary dysplasia, 210
  neonatal respiratory distress syndrome as cause, 627
“Brown” bone tumor, 657
Brown-Séquard syndrome, **501**
  Horner syndrome, 509
Brucella spp
  Gram-negative algorithm, 137
  intracellular organism, 124
  taxonomy, 121
  transmission, 144
Brucellosis, 144
Brugada syndrome, **283**, 293
Bruising
  child abuse sign, 526
  scurvy, 65
Brunner glands
  duodenum, 347
  ulcers and, 363
Brushfield spots, 59
Bruton agammaglobulinemia, 56, 112
Bruxism, 467
BTK gene, 112
Budd-Chiari syndrome, **375**
  labs/findings, 659
  portal hypertension, 372
  presentation, 652
Budesonide, 649
Buerger disease, **302**
  associations with, 667
  treatment, 661
Buffalo hump, 323
Bulbus cordis, 268
Bulimia nervosa, 537
  anovulation and, 609
  drug therapy for, 542
  Mallory-Weiss syndrome and, 360
  SSRIs for, 545
  treatment, 661
Bulk-forming laxatives, 383
Bullae, 447
  necrotizing fasciitis, 451
  Stevens-Johnson syndrome, 452
Bull neck, 128
Bullous impetigo, 451
Bullous pemphigoid, 447, 452
  autoantibody, 111
  type II hypersensitivity, 108
Bumetanide, **575**
BUN (blood urea nitrogen)
  intrinsic renal failure, 571
  nephritic syndrome, 563
  ornithine transcarbamylase deficiency, 79
  renal failure consequences, 571
BUN/creatinine ratio, 571
Bundle of His, 282
Bunyaviruses
  characteristics of, 163, 164
Bupivacaine, 519
Buprenorphine
  heroin addiction, 541
  morphine and, 228
  opioid withdrawal, 540
Bupropion, 546
  major depressive disorder, 531
  mechanism, 544
  nicotine withdrawal, 540
  seizures with, 242
Burkholderia cepacia
  characteristics of, 124
  cystic fibrosis, 175
  immunodeficiency infections, 114
  taxonomy, 121
Burkitt lymphoma, 408
  chromosomal translocations and, 412
  EBV, 161
  labs/findings, 660, 668
  oncogenes and, 218
  oncogenic microbes and, 219
Burns
  acute gastric ulcer, 664
  child abuse sign, 526
  inhalational injuries and, 640
  shock with, 299
  sunburn, 453
  testosterone/methyltestosterone for, 623
Bursitis
  prepatellar, 425
Burton line
  lead poisoning, 397
  presentation, 652
Buspirone, **544**
  generalized anxiety disorder, 533
Busulfan, 418
  pulmonary fibrosis and, 242
Busulfan toxicity, 422
  restrictive lung disease, 639
Butorphanol, **521**
Butterfly facial rash, 652

C

C1 esterase inhibitor deficiency, 103
C3 deficiency, 103
C5a receptor, 386
C5-C9 deficiencies, 103
CA 15-3/CA27-29 (tumor markers), 220
CA 19-9 (tumor marker), 220
CA 125 levels, 610
CA 125 (tumor marker), 220
Cachexia, **221**
  TNF-α and, 104
Café-au-lait spots
  aplastic anemia and, 399
  causes of, 652
  McCune-Albright syndrome, 53
  neurofibromatosis, 495
Caffeine intoxication and withdrawal, 540
Cahill cycle, 78
Caisson disease, 637
Calciferol (vitamin D), 559
Calcification, **208**
Calcineurin, 116
Calcinosis, 446
Calcitonin, **321**
  medullary thyroid carcinoma production, 330
  osteoporosis, 435
  signaling pathways of, 322
  tumor marker, 220
Calcium
  in bone disorders, 437
  calcitonin and, 321
  in cardiac muscle, 280
  in osteomalacia/rickets, 436
  in Paget disease of bone, 436
  PTH and, 320
  rhomboid crystals, 660
  Vitamin D and, 319
Calcium carbonate, 382
Calcium channel blockers, **304**
  angina, 304
  antiarrhythmic drugs, **310**
  contractility in, 273
  cutaneous flushing, 239
  gingival hyperplasia, 241
  hypertension, 304
  hypertrophic cardiomyopathy, 297
  migraine headaches, 488
  Raynaud phenomenon, 445
Calcium channels
  ethosuximide effect on, 514
  glucose and, 314
  Lambert-Eaton myasthenic syndrome and, 217
  myocardial action potential, 280
  opioid effect on, 520
  pacemaker action potential, 281
  smooth muscle contraction, 434
Calcium homeostasis, **319**
Calcium oxalate nephrolithiasis, 65
Calcium pyrophosphate deposition disease, **440**
Calcium-sensing receptor (CaSR), 342
Calf pseudohypertrophy, 652
Caliciviruses
  characteristics of, 159, 163
California encephalitis, 163
Call-Exner bodies, 611
Calluses (dermatology), 448
cAMP (cyclic adenosine monophosphate)
  cilostazol/dipyridamole effect on, 415
  endocrine hormone messenger, 322
  exotoxin effects, 128
  fructose bisphosphatase-2 and, 72
  glycogen regulation, 81
  heat-labile/heat-stable toxin effects, 128
  hyperparathyroidism, 332
  PTH effect on, 320
  Vibrio cholerae, 141
CAMP factor, 133
Campylobacter spp
  animal transmission, 144
  bloody diarrhea, 175
  reactive arthritis and, 442
  taxonomy, 121
Campylobacter jejuni, **140**
  Gram-negative algorithm, 137
  Guillain-Barré syndrome, 493
Canagliflozin, 341
Canalicular lung development, 626
Cancer
  bacteremia with, 660
  deaths from, **260**
  common metastases, 221
  epidemiology of, 216
  ESR in, 212
  intron/exon splicing variants and, 39
  microRNAs and, 39
  mortality of, 216
  neoplastic progression, 215
  pneumoconioses, 641
  splice site mutations as cause, 36
Cancer drugs
  cell cycle, **416**
  targets, **416**
Cancer epidemiology, **216**
Candesartan, 577
Candida spp
  amphotericin B, 195
  azoles, 195
  catalase-positive organism, 124
  echinocandins, 196
  immunodeficiency infections, 114
  osteomyelitis, 176
  tricuspid valve endocarditis and, 299
  vulvovaginitis, 177
Candida albicans, **149**
  HIV-positive adults, 173
  T cell dysfunction, 112
  treatment, 661
Candidate identification number (CIN), 5
Candidiasis
  Candida albicans, 149
  chronic mucocutaneous, 112
  cortisol and, 319
  nystatin, 195
Cannibalism, 174
Capillary fluid exchange, **287**, 670
Capillary supply (lymph node), 92
Capitate bone, 426
Capitation, 260
Caplan syndrome, 641
Capsid (viral), 158
Capsules (bacterial), 120
Captain’s wheel, 147
Captopril, 577
Caput medusae, 350
Carbachol, 232
  glaucoma, 521
Carbamazepine
  agranulocytosis, 241
  aplastic anemia, 241
  bipolar disorder, 531, 661

Carbamazepine *(continued)*
  cytochrome P-450 and, 243
  epilepsy, 514
  SIADH and, 240
  teratogenicity, 582
  tonic-clonic seizures, 663
  trigeminal neuralgia, 664
Carbamoyl phosphate, 78
Carbamoyl phosphate synthetase, 69
Carbapenems
  mechanism and use, **186**
  mechanism (diagram), **183**
  Pseudomonas aeruginosa, 139
Carbidopa, **518**
Carbohydrate absorption, **358**
Carbon dioxide
  transport of, **635**
Carbonic anhydrase, 635
Carbonic anhydrase inhibitors, 562
Carbon monoxide (CO)
  carboxyhemoglobin, 632
  electron transport inhibition, 74
  inhalational injuries, 640
  poisoning, 633
  toxicity treatment, 239
Carbon tetrachloride
  as carcinogen, 219
  free radical injury and, 210
Carboplatin, **419**
  toxicities of, 422
Carboxyhemoglobin, 632
Carboxylases, 69
Carboxypeptidase, 358
Carcinoembryonic antigen (CEA) (tumor marker), 220
Carcinogens, **219**
  griseofulvin, 196
Carcinoid syndrome, **338**
  bronchial carcinoid tumors, 647
  somatostatin for, 342
  treatment, 661
Carcinoid tumors
  octreotide for, 382
  stomach, 362
Carcinoma in situ, 215
Carcinomas
  bone, 437
  colorectal, 372
  invasive, 215
  metastases of, 215, 221
  nomenclature of, 216
  primary hyperparathyroidism, 331
  thyroid, 330
Cardiac arrest
  hypermagnesemia, 560
Cardiac cycle, **276**
Cardiac depression, 304
Cardiac function curves, **275**
Cardiac glycosides, **307**
Cardiac looping, 268
Cardiac muscle innervation, 229
Cardiac output, **272**
  equation for, 669
  exercise and, 635
  in pregnancy, 598
  variables in, 273
  $\dot{V}/\dot{Q}$ mismatch and, 634
Cardiac tamponade, **300**
  aortic dissection and, 293
  jugular venous pulse in, 276
  MI, 294, 296
  pulse pressure in, 272
  shock, 299
Cardiac troponin I, 295
Cardiac tumors, **301**
Cardinal ligament, 592
Cardinal veins, 268
Cardiobacterium spp, 299
Cardiogenic shock
  MI, 294
  presentation/treatment, 299
  pulse pressure in, 272
Cardiomegaly
  Pompe disease, 83
Cardiomegaly with apical trophy, 658
Cardiomyopathy, **296**
  auscultation changes with, 278
  Chagas disease, 154
  heart failure with, 298
  Kussmaul sign in, 301
  S4 heart sound and, 668
  Starling curves, 274
  sudden cardiac death, 293
Cardiotoxicity
  doxorubicin, 418
  drugs causing, 422
  methylxanthines, 649
  trastuzumab, 421
Cardiovascular drugs
  naming conventions for, 244
  reactions to, **239**
Cardiovascular system, **268–310**
  anatomy, 271
  embryology, 268–270
  pathology, 288–303
  pharmacology, 304–310
  physiology, 272–287
  sclerosis of, 446
Carditis
  Lyme disease, 142
  rheumatic fever, 132, 300
  Streptococcus pyogenes, 132
Carfilzomib, 420
Carmustine, 418
  in cell cycle, 416
  pulmonary fibrosis, 242
Carnitine, 85
Carnitine acyltransferase I, 69
Carotid artery
  atherosclerosis in, 292, 668
  bifurcation landmark, 629
  embryonic development, 586
  giant cell arteritis and, 302
Carotid artery (internal)
  cavernous sinus, 512
  circle of Willis, 473
  emboli from, 507
Carotid sinus, 285
Carpal bones, 426
Carpal tunnel syndrome, **426**
  lunate disclocation, 426
  median nerve injury, 427
  rheumatoid arthritis, 439
Car seats for children, 258
Carteolol, 521
Cartilage
  collagen in, 46
  fluoroquinolone damage to, 241
Carvedilol, 237, 309
Casal necklace, 63
Caseating granulomas, 139
Caseating necrosis, 205
  granulomatous diseases and, 211
Case-control studies, 246
Caspases, 204
Caspofungin
  Candida albicans, 149, 661
  echinocandins, 196
  mechanism (diagram), 194
Casts in urine, **562**
Catabolism
  amino acids, 78
  fatty acids, 43
  tyrosine, 79
Catalase, 210
Catalase-positive organisms, **124**
Cataracts, **505**
  corticosteroid toxicity, 116
  diabetes mellitus and, 336
  galactosemia, 76
  muscular dystrophy, 57
  rubella, 178
  sorbitol, 77
Catecholamines
  adrenal medulla secretion, 312
  amphetamines and, 234
  contractility effects of, 273
  ephedrine and, 234
  pacemaker action potential and, 281
  pheochromocytoma effect on, 326
  synthesis of, **79**
Cat scratch disease, 144
  as granulomatous disease, 211
Cats, (disease vectors)
  Campylobacter jejuni, 140
  osteomyelitis, 176
  Pasteurella multocida, 144, 182
  Tinea corporis, 148
  Toxoplasma gondii, 152, 178
Cauda equina syndrome, **500**
Caudal fold closure defects, 344
Caudal regression system, 582
Caudate
  basal ganglia (diagram), 470
  Huntington disease, 490
Cause-and-effect diagram, 262
Cavernous hemangiomas, 375
Cavernous sinus, **512**
  dural venous sinuses, 473
Cavernous sinus syndrome, 512
CBSSA to USMLE score prediction, 14
CCR5 protein
  HIV and, 171
  maraviroc, 199
  viral receptor, 162
CD4 protein
  viral receptor, 162
CD4+ T cells (HIV), 172
CD5 protein, 410
CD20 protein, 106
  in CLL, 410
CD21 protein, 106
  viral receptor, 162
CD25 protein
  cell surface protein, 106
  regulatory T cells and, 98
CD28 protein, 106
CD34 protein, 106
  leukocyte extravasation and, 209
CD40L protein, 106
CD40 protein, 106
CDKN2A gene, 218
CEA tumor marker, 371
Cefaclor, 185
Cefazolin
  mechanism and use, 185
  prophylaxis, 194
Cefepime
  mechanism and use, 185
  mechanism (diagram), 183
  Pseudomonas aeruginosa, 139
Cefotaxime, 185
Cefoxitin
  mechanism and use, 185
  mechanism (diagram), 183
Ceftaroline
  mechanism and use, 185
  mechanism (diagram), 183
  MRSA, 194
Ceftazidime
  mechanism and use, 185
  Pseudomonas aeruginosa, 139
Ceftriaxone
  Chlamydia spp, 146
  Chlamydia trachomatis, 661
  for gonococci, 138
  for *Haemophilus influenzae*, 138
  mechanism and use, 185
  mechanism (diagram), 183
  meningitis, 176
  meningococci, 138
  prophylaxis, 194
  typhoid fever, 141
Cefuroxime
  mechanism and use, 185
Celecoxib, 243, **456**
  arachidonic acid pathway, 455
Celiac artery
  mesenteric ischemia, 369
  structures supplied, 348
Celiac disease, **364**
  antibodies in, 657
  autoantibodies with, 111
  biliary cirrhosis and, 378
  dermatitis herpetiformis, 452
  HLA genes and, 96
  IgA deficiency, 112
Celiac lymph nodes, 93
Celiac trunk, 348, **349**
Cell cycle phases, **42**
Cell envelope (bacterial), 120
Cell injury, **206**
Cell lysis, 560
Cell membrane
  apoptosis and, 204

Cell surface proteins
  association and functions, **106**
  leukocyte adhesion deficiency, 113
  T cells and, 97, 98
Cell trafficking, **43**
Cellular biochemistry, **42–48**
Cellular inflammation, 207
Cellulitis, 451
  Pasteurella multocida, 144
  Streptococcus pyogenes, 132
Cell walls
  bacterial, **120**
Central canal of spinal cord, 478
Central clearing, 148
Central clearing (nuclei), 330
Central diabetes insipidus, 334
Central nervous system (CNS), **229**
  anesthetic principles for, 518
  antiarrhythmic adverse effects, 308, 309
  depression, 515
  nitrosoureas effect on, 418
  origins of, **460**
  shock from injury, 299
Central pontine myelinolysis. *See* Osmotic demyelination syndrome
Central post-stroke pain syndrome, **485**
Central retinal artery occlusion, **507**
  “cherry-red” macular spot, 652
Central sleep apnea, 642
Central sulcus, 471
Central tendency measures, 251
Central tendon (diaphragm), 629
Central vein, 206
Central vertigo, 503
Centriacinar emphysema, 638
Centrilobular necrosis, 219
Centromer autoantibodies, 111
Cephalexin
  mechanism and use, 185
Cephalosporins
  disulfram-like reaction, 242
  mechanism and use, **185**
  mechanism (diagram), 183
  pseudomembranous colitis, 240
  Pseudomonas aeruginosa, 139
Cephazolin, 183
Ceramide, 84
Ceramide trihexoside, 84
Cerebellum, **469**
  development of, 460
  hemisphere lesions, 481
  tonsils, 462
  vermis lesions, 462, 481
Cerebral aqueduct of Sylvius, 474
Cerebral arteries
  cavernous sinus, 512
  cortical distribution, **472**
Cerebral cortex
  arterial distribution, 471
  functional areas of, **471**
Cerebral edema
  diabetic ketoacidosis and, 337
  hyperammonemia, 78
  therapeutic hyperventilation, 472
Cerebral hemispheres, 460
Cerebral infarct, 529
Cerebral peduncle, 474
Cerebral perfusion, **472**
Cerebral perfusion pressure, 472
Cerebrospinal fluid (CSF)
  blood-brain barrier and, 466
  circulation of, 465, 473, 491
  Guillain-Barré syndrome, 493
  hydrocephalus, 492
  multiple sclerosis, 493
  neural tube defects, 461
  neurodegenerative disorders, 491
  origins, 460
  poliomyelitis, 501
  spinal cord, 478
  ventricular system, 474
  yellowish tint, 661
Cerebrovascular disease
  diabetes mellitus, 336
Cereulide, 134
Certolizumab, 118
Ceruloplasmin
  free radical elimination by, 210
Cervical cancer, 609
  carcinogens causing, 219
  epidemiology of, 608
  epithelial histology, 592
  HIV-positive adults, 173
  hydronephrosis from, 568
  oncogenic microbes and, 219
  papillomaviruses, 160
Cervical dysplasia, 609
Cervical lymphadenopathy, 652
Cervical lymph nodes, 93
Cervical rib, 428
Cervicitis
  sexually transmited infections, **180**
Cervix
  anatomy of, 592
  lymphatic drainage of, 591
  pathology of, **609**
Cestodes, **156**
Cetirizine, 648
Cetuximab, 118, **420**
CFTR gene, 56
  chronic pancreatitis and, 380
cGMP (cyclic guanosine monophosphate)
  atrial natriuretic peptide and, 285
  endocrine hormone messenger, 322
  hydralazine and, 304
  male sexual response, 593
  PDE-5 inhibitors, effect on, 623
  smooth muscle contraction, 434
Chagas disease, 154
  achalasia in, 360
  cardiomyopathy in, 297
  labs/findings, 658
Chancroids, 180
Chandelier sign, 181
Chaperone protein, **41**
Charcoal yeast extract culture
  Legionella pneumophila, 123, 139
Charcot-Bouchard microaneurysms, 483, 486
Charcot joints
  syphilis, 143
  tabes dorsalis and, 500
Charcot-Leyden crystals, 638
Charcot-Marie-Tooth disease, 494
Charcot triad, 379, 493
Charging, tRNA, 40
Chédiak-Higashi syndrome, 113
Cheilosis, 63
Chelation
  hemochromatosis, 378
  iron poisoning, 404
  lead poisoning, 397
Chemical tracheobronchitis, 640
Chemokines, 104
Chemoreceptors, **285**
Chemotherapy
  AML and, 410
  malignant bone tumors, 438
  myelodysplastic syndromes, 409
  neutropenia with, 402
  ondansetron, 383
  pancreatic cancer, 380
  readmissions with, 261
Chemotoxicities, **422**
Cherry hemangiomas, 450
Cherry-red macular spot
  diagnoses with, 652
Cherry-red spot (macula), 507
  lysosomal storage disease, 84
Chest pain
  Dressler syndrome, 652
  on exertion, 652
  panic disorder, 533
  pneumothorax, 644
  pulmonary embolism, 637
Chest wall
  elastic properties, **631**
Chest X-rays
  aortic dissections on, 293
  balloon heart on, 297
  eggshell calcification, 641
  lung abscesses, 646
  notched ribs on, 289
  Wegener granulomatosis on, 302
Chiari malformations, 462
Chickenpox
  rash, 179
  VZV, 160
Child abuse, **526**
  osteogenesis imperfecta and, 47
Childbirth
  Budd-Chiari syndrome and, 375
  contraction prevention, 595
  endometritis after, 612
  Graves disease and, 329
  low birth weight, 599
  misoprostol induction, 382
  neonatal flora, 174
  oxytocin, 599
  oxytocin for induction of, 342
  postpartum mood disturbances, **532**
  preterm, as common cause of death, 260
  progesterone levels after, 595
  Sheehan syndrome after, 335
  stress incontinence and, 569
Childhood disorders, **527**
Child neglect, **526**
Children
  car seats for, 258
  developmental milestones, **258**
Chimeric monoclonal A_b, 244
Chipmunk facies, 397
Chi-square tests, 253
Chlamydia spp, **146**
  atypical infections, 175
  Giemsa stain, 122
  intracellular organism, 124
  macrolides, 189
  pneumonia, 645
  reactive arthritis, 442
  sulfonamides for, 190
  taxonomy, 121
  tetracyclines, 188
Chlamydia, 180
Chlamydia trachomatis, 146
  eosiinophilia, 146
  pelvic inflammatory disease, 181
  pneumonia, 175
  treatment, 661
  UTIs, 570
Chlamydophila pneumoniae, 146
  pneumonia, 175
Chlamydophila psittaci, 146
  transmission, 144
Chloasma, 448
Chloramphenicol, **188**
  aplastic anemia and, 241, 399
  gray baby syndrome, 241
  mechanism (diagram), 183
  pregnancy, 201
  protein synthesis inhibition, 187
Chlordiazepoxide, 515
  alcohol withdrawal, 542
Chlorhexidine, 200
Chloride channels
  cystic fibrosis, 56
Chloroquine, **196**
  malaria, 153
Chlorpheniramine, **648**
Chlorpromazine, 543
Chlorpropamide, 340
Chlorthalidone, 576
Chocolate agar
  Haemophilus influenzae, 123, 138
Chocolate-colored blood, 632
Chocolate cysts, 610, 613
Cholangiocarcinomas
  Clonorchis sinensis, 156, 157
  hyperbilirubinemia, 376
  oncogenic microbes and, 219
  sclerosing cholangitis, 378
Cholangitis, 379
Cholecalciferol, **319**. *See also* Vitamin D
Cholecystectomy
  cholelithiasis, 379
  porcelain gallbladder, 379
Cholecystitis, 379
Cholecystokinin (CCK)
  functions, 356
  secretory cell location, 357

Cholelithiasis, **379**
  acute pancreatitis, 380
  bile ducts and, 353
  biliary cirrhosis and, 378
  Crohn disease, 365
  hyperbilirubinemia and, 376
  octreotide and, 382
  somatostatinomas, 338
Cholera toxin
  lysogenic phage infection, 126
  mechanism, 128
Cholestasis serum markers, 373
Cholesteatomas, **503**
Cholesterol
  atherosclerosis, 292
  in bile, 358
  cholelithiasis and, 379
  functions, 46
  hyperlipidemia signs, 291
  lipid-lowering agents, 306
  synthesis of, 69
  vitamin B_3 effects, 63
Cholesterol desmolase, 318
Cholesterol ester transfer protein (CETP), 88
Cholestyramine, 306
Choline, 231
Cholinergic agonists, 244
Cholinergic drugs, 231
Cholinergic effects, 307
Cholinesterase inhibitors
  diarrhea with, 240
  poisoning from, **232**
Cholinomimetic agents, **232**, 521
Chondrocalcinosis, 440
Chondrocytes
  achondroplasia, 435
  bone formation and, 434
  osteoarthritis, 439
Chondrosarcomas, 438
Chordae rupture, 279
Chorea
  brain lesions, 481
  Huntington disease, 490
  movement disorders, 489
Choriocarcinomas, **605**
  hCG in, 598
  hydatidform mole, 605
  methotrexate for, 417
  testicular tumors, 618
  theca-lutein cysts and, 610
Choriod (ophthalmology)
  closure of, 506
Chorionic plate, 584
Chorionic somatomammotropin, 598
Chorionic villi
  hydatidiform moles, 605
  placenta, 584
Chorioretinitis
  congenital toxoplasmosis, 152, 178
Choristomas, 216
Choroid (ophthalmology)
  inflammation, 506
  neovascularization, 506
  normal eye, 504
Choroid plexus (CNS), 474
Chromaffin cells
  Diagram, 312
  embryologic derivatives, 581
  pheochromocytomas, 326
Chromatin structure, **32**
Chromatolysis, **465**
Chromogranin A, 647
Chromosomal disorders, **60**
  karyotyping for, 51
Chromosomal translocations, **412**
Chronic adrenal insufficiency, 387
Chronic gastritis, 362
Chronic gout
  treatment, 661
Chronic granulomatous disease (CGD), **211**
  Aspergillus fumigatus, 149
  catalase-positive microbes, 182
  IFN-γ, 200
  immunodeficiencies and, 113
  recombinant cytokines for, 117
  respiratory burst in, 105
Chronic inflammation, 207
Chronic ischemic heart disease, 293
Chronic kidney disease
  in anemia taxonomy, 396
  erythropoietin in, 559
  focal segmental glomerulosclerosis, 566
  hypertension and, 290
Chronic lymphocytic leukemia (CLL), 410
  age ranges, 664
  immunosuppressants, 116
  lab findings, 661
  presentation, 655
  rituximab for, 420
  therapeutic antibodies, 118
Chronic mesenteric ischemia, 369
Chronic mucocutaneous candidiasis, 112
Chronic myelogenous leukemia (CML), 410
  age ranges, 664
  basophilia caused by, 387
  busulfan for, 418
  chromosomal translocations and, 412
  imatinib for, 420
  oncogenes and, 218
  Philadelphia chromosome, 668
Chronic myeloproliferative disorders, **411**
Chronic obstructive pulmonary disease (COPD)
  albuterol for, 234
  β-blockers and, 237
  cholinomimetic agents and, 232
  muscarinic antagonists for, 233
  salmeterol for, 234
Chronic pancreatitis, **380**
  pancreatic insufficiency from, 364
Chronic placental insufficiency, 548
Chronic pyelonephritis, 570
  labs/findings, 660
Chronic renal disease, 608
Chronic renal failure, 331, 571
  hypherphosphatemia with, 332
Chronic respiratory disease, as common cause of death, 260
Chronic thromboembolic pulmonary hypertension, 643
Chronic transplant rejection, 115
Churg-Strauss syndrome, **303**
  autoantibody with, 111
  as granulomatous disease, 211
  labs/findings, 657
Chvostek sign, 560
  hypoparathyroidism, 331
Chylomicrons, 88, 89
Chylothorax, 644
Chymotrypsin, 358
Cidofovir, **198**
Cigarette smoke (carcinogen), 219
Ciguatoxin, 238
Cilastatin
  imipenem and, 186
  seizures with, 242
Ciliary body, 504
Ciliary ganglia, 509
Cilia structure, **45**
Ciliated cells, 628
Cilostazol, **415**
Cimetidine, 381
  cytochrome P-450 and, 243
  gynecomastia, 615
Cinacalcet, **342**
Cinchonism
  antiarrhythmic causing, 308
  neurologic drug reaction, 242
Cingulate gyrus, 468
Cingulate herniation, 499
Ciprofloxacin
  for Crohn disease, 365
  cytochrome P-450 and, 243
  fluoroquinolnes, **191**
  mechanism (diagram), 183
  meningococci, 138
  Mycobacterium avium-intracellulare, 192
  prophylaxis, 194
  Pseudomonas aeruginosa, 139
Circadian rhythm
  hypothalamic control, 466
  sleep physiology, 467
Circle of Willis, **473**
  saccular aneurysms, 486
Circulatory system
  kidneys and, 550
Circulatory system (fetal), **270**
Cirrhosis, **372**
  α_1-antitrypsin deficiency, 375
  alcoholic, 67, 374
  autoantibody with, 111
  cholelithiasis and, 379
  cystic fibrosis, 56
  esophageal varices and, 360
  fructose intolerance, 76
  granulomatous disease, 211
  gynecomastia, 615
  hemochromatosis, 378
  hepatocellular carcinomas, 375
  loop diuretics for, 575
  non-alcoholic fatty liver disease, 374
  pleural effusion, 644
  portal hypertension, 372
  Wilson disease, 378
Cisplatin, **419**
  acute tubular necrosis, 572
  in cell cycle, 416
  Fanconi syndrome, 556
  targets of, 416
  toxicity of, 242, 422
Citalopram, 545
Citrate synthase, 70
Citrobacter spp
  Gram-negative algorithm, 137
  lactose fermentation, 138
Citrulline, 78
c-KIT gene, 218
CKK hormone, 325
CK-MB, 293, 295
Cladribine, 417
  in cell cycle, 416
  for hairy cell leukemia, 410
Clara cells, 627, 628
Clarithromycin
  Helicobacter pylori, 142
  HIV prophylaxis, 194
  macrolides, **189**
  mechanism (diagram), 183
  Mycobacterium avium-intracellulare, 192
  pregnancy use, 201
Clasp knife spasticity, 499
Classical conditioning, **524**
Class switching
  CD40, 99
  thymus-dependent antigens, 101
Clathrin, 43
Claudication
  atherosclerosis, 292
  Buerger disease, 302
  cilostazol/dipyridamole for, 415
  giant cell arteritis, 302
Clavulanate
  Haemophilus influenzae, 138
Clavulanic acid, 184
Clawing of hand, **429**
  Klumpke palsy, 428
Clearance of drugs, 225
Clear cell adenocarcinomas, 609
  DES and, 621
Cleft lip, 588
Cleft palate, **588**
  22q11 deletion syndromes, 61
  Patau syndrome, 59
  Pierre Robin sequence, 587
  teratogens for, 582
Clevidipine, 304
  for hypertensive emergency, 304
Clindamycin
  bacterial vaginosis, 144
  Clostridium difficile and, 134
  endometritis, 612
  lung abscesses, 646
  mechanism and use, **188**

  mechanism (diagram), 183
  metronidazole vs, 188
  protein synthesis inhibition, 187
  pseudomembranous colitis with, 240
Clinical reflexes, **480**
Clinical trials, 246
Clinical vignette strategies, 21
Clitoris
  genital homologs, 590
"Clock-face" chromatin, 389, 409
Clofazimine
  Hansen disease, 137
  Mycobacterium leprae, 192
Clomiphene
  estrogen receptor modulators, 621
  hot flashes with, 240
  PCOS, 609
  reproductive hormones and, 620
Clomipramine, 545
  obsessive-compulsive disorder, 533
Clonidine, 235
  Tourette syndrome, 527
Cloning methods (laboratory technique), **51**
Clonorchis sinensis
  diseases association, 157
  as oncogenic microbe, 219
  trematodes, **156**
Clonus
  serotonin syndrome, 545
Clopidogrel, 415
  acute coronary syndromes, 296
  for ischemic stroke, 482
  thrombogenesis and, 393
Closed-angle glaucoma, 506
  pilocarpine for, 232
Clostridium spp, **134**
  anaerobic organism, 123
  Gram-positive algorithm, 130
  taxonomy, 121
Clostridium botulinum, **134**
  exotoxin production, 128
  food poisoning, 174
  spore formation, 127
  therapeutic uses, 134
Clostridium difficile, **134**
  antibiotic use and, 134, 181
  metronidazole, 191
  nosocomial infection, 181
  presentation of, 652
  proton pump inhibitors and, 381
  spore formation, 127
  vancomycin, 186
  watery diarrhea, 175
Clostridium perfringens, **134**
  clindamycin, 188
  exotoxin production, 129
  food poisoning, 174
  spore-formation, 127
  traumatic open wound, 182
  watery diarrhea, 175
Clostridium tetani, **134**
  exotoxin production, 128
  spore formation, 127
Clotrimazole, 194, 195
Clotting factors, 66
Clozapine, 543
  agranulocytosis with, 241
Clubbing
  adenocarcinoma, 647
  bronchiectasis, 639
  Eisenmenger syndrome, 289
Clubbing (nails)
  cystic fibrosis, 56
Club cells, 627
Clue cells, 660
  bacterial vaginosis, 144, 177
Cluster A personality disorders, 535
Cluster B personality disorders, 535
Cluster C personality disorders, 535
Cluster headaches, 488, 516
c-MYC gene, 218
CNS lymphomas
  HIV-positive adults, 173
  oncogenic microbes and, 219
CNS stimulants, **542**
Coagulation, 66
Coagulation cascade, **392**
Coagulation disorders, **404**
  hereditary thrombosis syndromes, **406**
  platelet and coagulation, **406**
Coagulation pathways, **391**
Coagulative necrosis, 205
  MI, 294
Coagulopathy
  postpartum hemorrhage, 607
  preeclampsia, 608
Coal workers' pneumoconiosis, **641**
CoA production, 63, 68
Coarctation of aorta, **289**, 290
  Turner syndrome, 603
Cobblestone mucosa, 365
Cocaine, 519
  β-blockers and, 237
  cardiomyopathy, 297
  coronary vasospasm, 239
  intoxication and withdrawal, 540
  liver processing of, 352
  as noradrenergic drug, 231
  placental abruption, 606
  pulmonary arterial hypertension, 643
  sympathomimetic action, 234
  teratogenicity, 582
Coccidioides spp
  silver stain, 122
  treatment, 195
Coccidioidomycosis, **147**
  erythema nodosum and, 453
  HIV-positive adults, 173
Coccobacilli, 137
Coccus bacteria
  antibiotic tests, 130
  Gram stain identification, 130
  taxonomy, 121
Cochlea
  CN VIII, 476
  inner ear, 503
  presbycusis, 503
Codeine, 520
Codman triangle, 438, 660
Codominance, **52**
Codons
  genetic code features, 34
  start and stop, **37**
Cofactors
  apolipoproteins, 89
  biotin, 64, 69
  cobalamin, 65
  copper, 47
  Menkes disease, 47
  pantothenic acid, 63
  phenylketonuria, 80
  precursors to organic, 61
  pyridoxine, 63
  pyruvate dehydrogenase complex, 72
  riboflavin, 63
  TCA cycle, 73
  thiamine, 70
  vitamin K, 66
"Coffee bean" nuclei, 610
Cognitive behavioral therapy (CBT), 527
  acute stress disorder, 534
  ADHD, 527, 661
  adjustment disorder, 533
  for anxiety disorders, 532
  for atypical depression, 531
  binge eating disorder, 537
  body dysmorphic disorder, 533
  conduct disorder, 527
  generalized anxiety disorder, 533
  major depressive disorder, 531
  obsessive-compulsive disorder, 533
  oppositional defiant disorder, 527
  panic disorder, 533
  phobias, 533
  postpartum depression, 532
  PTSD, 534
Cohort studies, 246
  relative risk and, 248
Coin lesion (X-ray), 647
Colchicine
  acute gout attack, 661
  agranulocytosis, 241
  calcium pyrophosphate deposition disease, 440
  diarrhea with, 240
  gout, 440, 457
  microtubules and, 44
  myopathy with, 241
Cold agglutinin disease, 655
Cold agglutinins, 146
Cold autoimmune hemolytic anemia, 401
Colectomy
  adenomatous polyposis, 370
  inflammatory bowel disease, 365
Colesevelam, 306
Colestipol, 306
Colistin B, 139
Colitis
  Clostridium difficile, 134
  HIV-positive adults, 173
  oral vancomycin, 186
  pseudomembranous, 127, 175, 184, 188
Collagen
  aging, 48
  decreased/faulty production, 47
  osteoblasts and, 434
  in scar formation, 210
  synthesis/structure, **46**
  vitamin C, 65
  in wound healing, 211
Collagenase in neutrophils, 386
Collapsing pressure (alveoli), 627
Collecting tubules
  defects in, 556
  diuretics and, 574
  nephron physiology, 555
  potassium-sparing diuretics and, 576
Colles fracture, 435
Colliculi, 475
Colon
  histology of, 347
  ischemia in, 206
Colon cancer
  5-fluorouracil for, 417
  irinotecan/topotecan for, 419
  labs/findings, 660
  metastases of, 221
  oncogenes and, 218
  Staphylococcus gallolyticus and, 133
  tumor suppressor genes and, 218
Colonic ischemia, 369
Colonic polyps, **370**
Colorado tick fever, 163
Color blindness, 193
Colorectal cancer, **371**
  adenomatous polyposis and, 370
  bevacizumab for, 420
  cetuximab for, 420
  incidence/mortality in, 216
  labs/findings, 657
  Lynch syndrome, 37
  molecular pathogenesis of, **372**
  therapeutic antibodies, 118
  tumor suppressor genes and, 218
Colovesical fistulas, 366
Coltivirus, 163
Coma
  adrenoleukodystrophy, 494
  benzodiazepine adverse effect, 515
  hepatic encephalopathy, 374
  herniation syndromes, 499
  hyperosmolar hyperglycemia nonketotic syndrome, 338
  hyponatremia, 560
  rabies, 167
  reticular activating system, 481
  Reye syndrome, 373
  thyroid storm, 329
  Toxocara canis, 155
  Trypanosoma brucei, 152
Combined pathway for coagulation, 391
Comedocarcinomas, 616
Comma-shaped rods, 137
Common bile duct, 346, 353
Common cold, 164
Common peroneal nerve, 430

- Common variable immunodeficiency (CVID), 112
- Communicating hydrocephalus, 492
- Competence (bacterial genetics), 126
- Competitive agonists, 228
- Competitive inhibitors, 224
- Complement, **103**
  - activation inhibition, 131
  - binding of, 100
  - C-reactive protein, 102
  - disorders of, **103**
  - eculizumab, 118
  - endotoxin activation, 129
  - immunodeficiency infections, 114
  - immunoglobulin isotypes, **101**
  - innate immunity, 95
  - splenic dysfunction, 94
  - transplant rejection, 115
- Complement activation pathways, **103**
- Complementation (viral), 158
- Complex renal cysts, 573
- Compliance (lungs), 631
- Complications of pregnancy, **606–607**
- Comprehensive Basic Science Examination (CBSE), 10
- Comprehensive Basic Science Self-Assessment (CBSSA), 11
- Computer-Based Test (CBT)
  - environment of, 3–4
  - exam schedule for, 7–8
  - structure of, 3
- COMT inhibitors, 517
- Conditioning (psychological), 524
- Conduct disorder, 527
  - early onset disorder, 535
- Conducting zone (respiratory tree), 628
- Conduction aphasia, 486
- Conductive hearing loss, 503
- Condylomata acuminata, 449
  - IFN-α for, 200
  - sexual transmission, 180
- Condylomata lata
  - syphilis, 143, 180
- Confidence intervals, 252
- Confidentiality, **255**
- Confluence of the sinuses, 473
- Confounding bias, 250
- Congenital adrenal hyperplasias, **318**
- Congenital heart disease, **288–290**
  - autosomal trisomies, 59
  - defect associations, **290**
  - maternal phenylketonuria, 80
  - pulmonary arterial hypertension, 643
  - rubella, 178
  - Turner syndrome, 656
- Congenital hydroceles, 618
- Congenital hypothyroidism, 328
- Congenital long QT syndrome, **283**
- Congenital lung malformations, **626**
- Congenital nevus, 447
- Congenital rubella
  - cardiac defect associations, 290
  - heart murmur, 279
- Congenital solitary functioning kidney, **549**
- Congenital syphilis, 143
- Congenital toxoplasmosis, 152
- Congo red stain, 213, 566
- Conivaptan
  - ADH antagonists, 334
  - SIADH, **342**
- Conjoined tendon, 354
- Conjugate vaccines, 124
- Conjugation (bacterial genetics), 126
- Conjunctival infections
  - Kawasaki disease, 302
- Conjunctivitis, **504**
  - adenoviridae, 160
  - chlamydia, 146, 180
  - gonococcal prophylaxis, 194
  - gonococci, 138
  - *Haemophilus influenzae*, 138
  - reactive arthritis, 442
  - rubeola, 166, 179, 182
  - urethritis and, 656
  - Zika virus, 167
- Connective tissue diseases
  - aortic dissection and, 293
  - pulmonary arterial hypertension, 643
  - thoracic aortic aneurysms and, 292
- Connective tissue drug reactions, **241**
- Conn syndrome, 324
- Consent
  - healthcare proxy, 257
  - minors, **254**, 256
- Consolidation (lung finding), 643
- Constipation, 520
  - aluminum hydroxide as cause, 382
  - anal fissures, 351
  - calcium channel blockers, 304
  - Hirschsprung disease, 367
  - hypothyroidism, 327
  - irritable bowel syndrome, 366
  - loperamide, 382
  - ondansetron, 383
  - ranolazine, 305
  - vincristine, 419
- Constrictive pericarditis
  - jugular venous pulse in, 276
  - Kussmaul sign, 301
- Contact activation pathway for coagulation, 391
- Contact dermatitis, 109
- Contemplation stage, 539
- Continuous heart murmurs, 279
- Contraception
  - isotretinoin teratogenicity, 582
  - methods for, **622**
  - parental consent for minors and, 254
- Contractility in cardiac output, 273
- Contraction alkalosis, 56
- Conversion disorder, 536
- Coombs hemolysis, 235
- Coombs-positive hemolysis
  - α-methyldopa, 235
  - anemia with, 241
- Coombs-positive hemolytic anemia, 401
- Coombs test, 108, 401
- COPI/COPII, 43
- Copper deficiency, 397
- Copper intrauterine device, **622**
- Copper toxicity, 239
- Coprolalia, 527
- Copy number variations (CNV), 50
- Cord factor, 136
- Cori cycle, 78
- Cori disease, 83
- Corkscrew fibers, 498
- Cornea, 504
  - collagen in, 46
- Corneal arcus
  - familial hypercholesterolemia, 90
  - hyperlipidemia, 291
- Corneal reflex, 477
- Corneal vascularization, 63
- Corniculate cartilage, 587
- Coronary aneurysms, 652
- Coronary arteries
  - anatomy of, **271**
  - atherosclerosis in, 292
  - occlusion of, 271
- Coronary artery
  - atherosclerosis in, 668
- Coronary artery disease
  - atrial fibrillation and, 284
  - diabetes mellitus and, 336
  - HMG-CoA reductase inhibitors for, 306
  - hormonal contraception contraindication, 622
  - hypertension and, 290
  - menopause and, 600
  - sudden cardiac death, 293
- Coronary sinus
  - anomalous pulmonary return, 288
  - development, 268
- Coronary steal syndrome, 293
- Coronary vasospasm, 239
- Coronaviruses
  - characteristics of, 163
  - genomes of, 159
- Cor pulmonale, 298, 633, 668
  - obstructive lung disease, 638
  - pneumoconioses, 641
  - pulmonary hypertension, 643
  - right ventricular failure, 633
- Corpus albicans, 597
- Corpus cavernosum
  - female homolog of, 590
  - lymphatic drainage of, 591
- Corpus luteum, 597
  - hCG and, 598
  - progesterone production, 595
- Corpus spongiosum, 590
- Correct results, in statistical hypothesis testing, 252
- Correlation coefficient, 253
- Corticosteroids
  - asthma, 649
  - cataracts, 505
  - CN VII paralysis, 502
  - Crohn disease, 365
  - Cushing syndrome, 323
  - giant cell arteritis, 302
  - hyperglycemia with, 240
  - hypopituitarism, 335
  - immunosuppression, 116
  - lymphopenia with, 402
  - microscopic polyangiitis, 302
  - minimal change disease, 566
  - neutrophilia from, 402
  - osteonecrosis, 436
  - osteoporosis with, 241
  - pancreatitis with, 240
  - polyarteritis nodosa, 302
  - for polymyalgia rheumatica, 444
  - syndrome of apparent mineralocorticoid excess, 556
  - Takayasu arteritis, 302
  - targets of, 117
  - thyroid storm, 329
  - Wegener granulomatosis, 302
- Corticotropin-releasing hormone (CRH), **315**
  - adrenal cortex regulation of, 312
  - cortisol regulation, 319
  - Cushing syndrome and, 323
  - signaling pathways of, 322
- Cortisol, **319**
  - adrenal cortex secretion, 312
  - congenital adrenal hyperplasias and, 318
  - in Cushing syndrome, 323
  - primary adrenal insufficiency, 324
  - signaling pathways for, 322
- Cortisone, 455
- *Corynebacterium* spp
  - Gram-positive algorithm, 130
  - taxonomy, 121
- *Corynebacterium diphtheriae*, **135**
  - culture requirements for, 123
  - exotoxin production, 128
  - unvaccinated children, 182
- Cough, 520
  - ACE inhibitors, 242, 577
  - asthma, 638
  - chronic bronchitis, 638
  - gastroesophageal reflux disease, 360
  - guaifenesin, 648
  - lung cancer, 647
  - Wegener granulomatosis, 302
- Councilman bodies
  - yellow fever, 164
- Countertransference, **524**
- Courvoisier sign
  - pancreatic cancer, 380
- Cowper gland, 593
- Cowpox, 160
- *Coxiella* spp, 124
- *Coxiella burnetii*
  - animal transmission, 144
  - endocarditis caused by, 299
  - Q fever, 145
  - spore formation, 127
- Coxsackievirus
  - acute pericarditis, 300
  - picornavirus, 164
  - presentation, 163
  - type A rash, 179

Coxsackievirus type B cardiomyopathy, 297
C-peptide
  insulin and, 314
  in insulinomas, 338
Cranial nerves, 285, **476**
  branchial arch derivation, 587
  common lesions, **502**
  impingement of, 435
  nerve and vessel pathways, **476**
  nuclei of, **475**
  reflexes of, **477**
Craniopharyngioma, 498
Craniopharyngiomas, 581
  hypopituitarism with, 335
Craniotabes, 436
C-reactive protein (CRP)
  acute-phase reactants, 102
  innate immunity and, 95
  osteomyelitis, 176
Creatine, 79
Creatine kinase, 199
Creatinine
  ACE inhibitor effects, 577
  acute renal failure, 571
  glomerular filtration rate and, 552
  nephritic syndrome, 563
  proximal convoluted tubules, 557
Creatinine clearance, 552
Cre-lox system, 52
Cremasteric muscle and fascia, 354
Crepitus in necrotizing fasciitis, 451
CREST syndrome, 446
  biliary cirrhosis and, 378
  Raynaud phenomenon, 445
CREST syndrome autoantibodies, 111
Cretinism, 328, 582
Creutzfeldt-Jakob disease, 174, 491
  dementia, 529
“Crew cut” (skull X-ray), 397, 400
CRH. *See* Corticotropin-releasing hormone (CRH)
Cribriform plate, 476
Cricoid cartilage, 587
Cricothyroid muscle, 587
Cri-du-chat syndrome, **60**
Crigler-Najjar syndrome, 376, 377
  presentation, 656
Crimean-Congo hemorrhagic fever, 163
Crohn disease, 365
  azathioprine, 116
  B_{12} deficiency, 398
  cholelithiasis and, 379
  as granulomatous disease, 211
  lesions in, 664
  natalizumab, 118
  spondyloarthritis and, 442
  sulfasalazine for, 382
  vitamin B_{12} deficiency, 65
Crossover studies, 250
Cross-sectional studies, **246**
Croup, **166**
  labs/findings, 660
  paramyxoviruses, 163, 165
  pulsus paradoxus in, 300
CRP and ESR, 212
Crust (skin), 447
Cryoprecipitate, 407
Crypt hyperplasia, 364
Cryptococcal meningitis, 195
Cryptococcosis, 149
Cryptococcus spp
  meningitis, 176
  treatment, 195
  urease-positive, 124
Cryptococcus neoformans, **149**
  HIV-positive adults, 173
  stains for, 122
Cryptogenic organizing pneumonia, 645
Cryptorchidism, **617**
  hypospadias, 591
  Sertoli cells and, 594
  testicular tumors, 618
Cryptosporidium spp, **151**
  HIV-positive adults, 173
  hyper-IgM syndrome and, 113
  watery diarrhea, 175
Crypts of Lieberkühn, 347
C-section deliveries
  neonatal flora, 174
  neonatal respiratory distress syndrome, 627
Cuneiform cartilage, 587
Curling ulcers
  gastritis, 362
Currant jelly sputum, 140, 182
  Klebsiella pneumonia, 655
“Currant jelly” stools, 368, 369
Curschmann spirals, 638
Cushing disease, 323
Cushing-like symptoms
  protease inhibitors, 199
Cushing reaction, 285
Cushing syndrome, **323**
  acanthosis nigricans and, 453
  anovulation with, 609
  corticosteroids, 116
  paraneoplastic syndrome, 217
  small cell lung cancer, 647
Cushing ulcers
  gastritis, 362
Cutaneous anthrax, **133**
  edema toxin, 128
Cutaneous flushing
  carcinoid syndrome, 338
  drugs causing, 239
Cutaneous larva migrans, 155
Cutaneous leishmaniasis, 154
Cutaneous mycoses, **148**
Cutaneous paraneoplastic syndromes, 217
Cutis aplasia
  Patau syndrome, 59
CXCR4
  viral receptor, 162
CXCR4/CCR5 protein
  presence on cells, 106
Cyanide
  electron transport chain, 74
Cyanide poisoning
  induced methemoglobinemia, 632
  inhalation injury, 640
  nitroprusside, 304
  treatment for, 239
Cyanopia, 623
Cyanosis
  “blue babies,” 288
  “blue kids,” 289
  bronchitis, 638
  Eisenmenger syndrome, 289
  esophageal atresia, 344
  methemoglobinemia, 632
  patent ductus arteriosus, 289
  pulmonary hypertension, 643
  tetralogy of Fallot as cause, 288
Cyclin-CDK complexes, 42
Cyclin-dependent kinases (CDKs), 42
Cyclins, 42
Cyclobenzaprine, **520**
Cyclooxygenase
  aspirin effect on, 393
Cyclooxygenase inhibition
  irreversible, 456
  reversible, 455, 456
  selective, 456
Cyclophilin targets, 117
Cyclophosphamide, 418
  hemorrhagic cystitis with, 240
  microscopic polyangiitis, 302
  polyarteritis nodosa, 302
  SIADH caused by, 334
  SIADH with, 240
  toxicities of, 422
  transitional cell carcinoma and, 569
  Wegener granulomatosis, 302
Cycloplegia
  atropine, 233
  muscarinic antagonists for, 233
Cyclosporine
  gingival hyperplasia, 241
  gout, 241
  immunosuppressant, 116
  targets of, 117
Cyclothymic disorder, 530, 531
Cyproheptadine, 545
Cyproterone, 620
Cystathionine, 63
Cystathionine synthase deficiency, 80
Cysteine, 81
Cystic duct, 353
Cysticercosis, 156
Cystic fibrosis, **56**
  Aspergillus fumigatus, 149
  bronchiectasis, 639
  chromosome association, 60
  common organisms, 175
  meconium ileus in, 369
  N-acetylcysteine, 648
  pancreatic insufficiency, 364
  Pseudomonas aeruginosa, 139
  vitamin deficiencies and, 61
Cystic hygromas, 450
  Turner syndrome, 603
Cystine, 567
Cystinosis, 556
Cystinuria, **81**
Cystitis
  acute bacterial, 562, 570
  squamous cell carcinoma risk, 569
Cytarabine, 417
  in cell cycle, 416
Cytochrome C, 204
Cytochrome P-450
  azoles, 195
  barbiturates and, 515
  cimetidine and, 381
  epilepsy drug effects on, 514
  griseofulvin, 196
  interactions with, 243
  macrolides, 189
  phenobarbital effect on, 514
  porphyria, 403
  rifamycins, 192
  ritonavir, 199
Cytokeratin
  cytoskeletal element, 44
  in epithelial cells, 447
Cytokine receptor, 218
Cytokines, **104**
  bacterial toxins, 106
  corticosteroids and, 116
  Graves disease and, 329
  recombinant, **117**
  rejection reactions, 115
  type IV hypersensitivity, 109
Cytokinesis, 42
Cytomegalovirus (CMV)
  AIDS retinitis, 161
  cholecystitis and, 379
  clinical significance, **161**
  esophagitis and, 360
  HIV-positive adults, 173
  hyper-IgM syndrome and, 113
  immunodeficient patients, 114
  pneumonia, 645
  retinitis and, 508
  ToRCHeS infection, 178
  treatment, 198
  viral receptor, 162
Cytoplasm
  cell cycle phase, 42
  cytoskeletal elements, 44
  glycolysis, 72
  HMP shunt, 75
  metabolism in, 68
Cytoplasmic membrane (bacterial), 120
Cytoplasmic processing bodies (P-bodies), 38
Cytosine methylation, 32
Cytoskeletal elements, **44**
Cytosol, 433
Cytotoxic T cells, **98**
  cell surface proteins, 106
  MHC I and II, 96
Cytotrophoblasts, 584
  choriocarcinomas and, 605

D

D_2 agonists, 543
D_2 antagonists, 543

- Daclizumab
  - immunosuppression, 116
  - targets of, 117
- Dacrocytes, 394
- Dactinomycin, 418
  - RNA polymerase inhibition, 38
  - targets of, 416
- Dactylitis
  - seronegative spondyloarthritis, 442
  - sickle cell anemia, 400
- Dalfopristin
  - mechanism (diagram), 183
  - VRE, 194
- Dalteparin, 413
- Danazol, **622**
  - endometriosis, 613
  - pseudotumor cerebri, 491
  - reproductive hormones and, 620
- Dandy-Walker syndrome, 462
- Dantrolene, 519, **520**, 543
- Dapagliflozin, 341
- Dapsone, **190**
  - dermatitis herpetiformis, 452
  - Hansen disease, 137
  - hemolysis in G6PD deficiency, 241
  - *Mycobacterium leprae*, 192
  - *Pneumocystis jirovecii*, 150
- Daptomycin, **191**
  - MRSA, 194
- Dark-field microscopy, 142
- Darunavir
  - HIV therapy, 199
  - mechanism (diagram), 197
- *Datura*, 233
- Daunorubicin, 418
  - dilated cardiomyopathy, 239
- *DCC* gene, 218
- D-dimer lab, 636
- Deafness
  - Alport syndrome, 565
  - congenital long QT syndrome, 283
  - congenital syphilis, 143
  - rubella, 178
  - syphilis, 178
- Deamination
  - base excision repair, 37
  - nucleotides, 33
- Death
  - aortic dissection in, 293
  - children, explaining to, 257
  - common causes, **260**
  - hyperosmolar hyperglycemia nonketotic syndrome, 338
  - sudden cardiac death, 293
  - thyroid storm, 329
- Debranching enzyme
  - Cori disease, 83
  - glycogen metabolism, 82
- Decay-accelerating factor (DAF), 103
- Deceleration injury, 292
- Decidua basalis, 584
- Decision-making capacity, 254
- Decompression sickness, 637
- Deep brachial artery, 432
- Deep inguinal lymph nodes, 591
- Deep inguinal ring, 354
- Deep venous thrombosis (DVT), **636**
  - direct factor Xa inhibitors for, 415
  - embolic stroke and, 482
  - glucagonomas and, 338
  - heparin for, 413
  - labs/findings, 659
  - tamoxifen/raloxifen and, 421
- Deer flies (disease vectors), 155
- Defensins, 95
- Deferasirox
  - hemochromatosis, 378
  - for iron poisoning, 239, 404
- Deferiprone
  - hemochromatosis, 378
  - for iron poisoning, 239
- Deferoxamine
  - hemochromatosis, 378
  - for iron poisoning, 239, 404
- Degenerate/redundant genetic code, **34**
- Degmacytes, 394
  - G6PD deficiency, 75
  - in G6PD deficiency, 400
- Dehydration
  - diabetic ketoacidosis, 337
  - DM type 2, 341
  - filtration changes and, 553
  - hyperosmolar hyperglycemic state, 338
  - loop diuretics and, 575
  - mannitol and, 575
  - shock, 299
- Dehydrogenases, 69
- Deiodinase, 321
- Delavirdine
  - HIV therapy, 199
  - mechanism (diagram), 197
- Delirium, **528**
  - barbiturate withdrawal, 540
  - dementia, 529
  - diabetic ketoacidosis, 337
  - PCP, 541
  - thyroid storm, 329
- Delirium tremens (DTs), **542**
  - alcohol withdrawal, 540, 541
- Δ cells
  - endocrine pancreas, 313
  - somatostatinomas of, 338
  - somatostatin production, 356
- Delta virus, 163
- Delta wave sleep, 467
- Deltoid muscle
  - axillary nerve injury, 427
  - Erb palsy, 428
- Delusional disorder, **530**
- Delusions, 529
  - mesolimbic pathway, 468
  - schizophrenia, 530
- Demeclocycline, **342**. *See also* Tetracyclines
  - diabetes insipidus and, 240, 334
  - for SIADH, 334
- Dementia, **529**
  - common brain lesions, 481
  - frontotemporal, 481
  - HIV-positive adults, 173
  - metachromatic leukodystrophy, 84, 494
  - neurodegenerative disorders, 490–491
  - Pick disease, 660
  - prion disease, 174
  - splice site mutations, 36
  - vitamin B_3 deficiency, 63
- Demyelination/dysmyelination
  - diseases of, **494**
  - vitamin B_{12} deficiency, 500
- Dendritic cells, **388**
  - IL-10, 104
  - innate immunity, 95
  - Langerhans cell histiocytosis and, 412
  - T- and B-cell activation, 97, 98, 99
- Dengue, 163
- Denial, 524
- Denosumab, 118
  - for osteoporosis, 435
- De novo pyrimidine and purine synthesis, **33**
  - rate-determining enzyme, 69
- Dense deposit disease, 565
- Dental caries, 132
- Dental plaque
  - normal flora, 174
  - viridans streptococci, 125
- Dentate line, 351
- Dentate nucleus, 469
- Dentin
  - collagen in, 46
  - osteogenesis imperfecta, 47
- Dentinogenesis imperfecta, 47
- Denys-Drash syndrome, 569
- Dependent personality disorder, 535
- Depersonalization/derealization disorder, 528
  - panic disorder, 533
- Depression
  - anorexia nervosa and, 537
  - atypical antipsychotics for, 543
  - atypical features in, **531**
  - benzodiazepine withdrawal, 540
  - dementia, 529
  - dissociative identity disorder, 528
  - drug therapy, 542
  - electroconvulsive therapy, 532
  - glucagonomas, 338
  - hyperparathyroidism, 332
  - marijuana withdrawal, 541
  - MDMA withdrawal, 541
  - metoclopramide, 383
  - mirtazapine for, 236
  - neurotransmitters for, 465
  - postpartum, 532
  - serotonin-norepinephrine reuptake inhibitors (SNRIs) for, 545
  - sexual dysfunction caused by, 537
  - SSRIs for, 545
  - stimulant withdrawal, 540
  - suicide and, 532
- Deprivation effects (infants), **526**
- De Quervain thyroiditis, 328
- *Dermacentor* tick (disease vector), 144
- Dermatitis
  - B-complex deficiency, 61
  - glucagonomas, 338
  - IPEX syndrome, 98
  - type IV hypersensitivity reaction, 109
  - vitamin B_5 deficiency, 63
  - vitamin B_7 deficiency, 64
- Dermatitis herpetiformis, 452
  - celiac disease and, 364
- Dermatology, 430–439, 446–454
  - macroscopic terms, **447**
  - microscopic terms, **448**
- Dermatomes
  - landmarks, **480**
- Dermatomyositis, **445**
  - autoantibody with, 111
- Dermatophytes, 148
- Dermatophytoses, 195
- Dermis, 446
- Dermoid cysts, 610
- Descending colon, 345
- Desert bumps, 147
- Desflurane, 519
- Desipramine, 545
- Desloratadine, 648
- Desmin, 44
- Desmoplakin, 447
- Desmopressin
  - for hemophilia, 404
- Desmopressin acetate
  - central DI, 317, 342
  - DI treatment, 334
- Desmosome, 447
  - autoantibody to, 111
- Desvenlafaxine, 545
- Detached retina, **507**
- Detemir insulin, 340. *See also* Insulin
- Detrusor instability, 569
- Developmental delays
  - renal failure and, 571
- Developmental milestones, 258
- Dexamethasone. *See also* Glucocorticoids
  - arachidonic acid pathway, 455
  - Cushing syndrom diagnosis, 323
- Dexlansoprazole, 381
- Dexrazoxane, 418
  - dilated cardiomyopathy prevention, 239
- Dextroamphetamine, 542
- Dextrocardia, 268
- Dextromethorphan, 520, **648**
- DHT, 604
- Diabetes insipidus, **334**
  - antidiuretic hormone in, 317
  - demeclocycline and, 342
  - desmopressin acetate for, 342
  - drug reaction and, 240
  - lithium, 544
  - potassium-sparing diuretics for, 576
  - thiazides for, 576
- Diabetes mellitus, **336–337**. *See also* Hyperglycemia
  - acanthosis nigricans, 453
  - atherosclerosis and, 292
  - atypical antipsychotics, 543
  - *beta-blockers* and, 237

  - binge eating disorder, 537
  - carpal tunnel syndrome, 426
  - cataracts and, 505
  - chronic renal failure and, 571
  - CN III damage, 511
  - diabetic ketoacidosis, 337
  - diabetic retinopathy, 507
  - drug therapy for, **340–341**
  - endometrial cancer risk, 612
  - Friedreich ataxia, 501
  - fungal infections, 182
  - glaucoma and, 506
  - glucagonomas, 338
  - glucosuria in, 554
  - hemochromatosis, 378
  - hepatitis C, 169
  - hypertension and, 290, 304
  - *Klebsiella*, 140
  - neonatal respiratory distress syndrome, 627
  - opportunistic infections, 149
  - pancreatic cancer, 380
  - polyhydramnios and, 607
  - preeclampsia and, 608
  - in pregnancy, 290
  - *Pseudomonas aeruginosa*, 139
  - pyelonephritis and, 570
  - readmissions with, 261
  - renal papillary necrosis and, 572
  - sexual dysfunction, 537
  - tacrolimus and, 116
  - teratogenic potential, 582
  - type 1 vs type 2, 337
  - urinary tract infections, 177
  - UTIs and, 570
- Diabetes mellitus type 1, **337**
  - autoantibody with, 111
  - HLA subtypes with, 96
  - treatments for, 340
- Diabetes mellitus type 2, **337**
  - hyperosmolar hyperglycemia nonketotic syndrome, 338
  - treatments for, 340
- Diabetic glomerulonephropathy, 566
- Diabetic ketoacidosis
  - black eschar, 652
  - ketone bodies, 86
  - metabolic acidosis, 561
- Diabetic ketoacidosis (DKA), **337**
  - DM type 1 and, 336
- Diabetic nephropathy
  - ACE inhibitors for, 577
  - angiotensin II receptor blockers for, 577
- Diabetic neuropathy, 545
- Diabetic retinopathy, **507**
- Diagnosis errors, 262
- Diagnostic maneuvers/signs
  - Gower sign, 57
- Diagnostic test evaluation, 247
- Dialectical behavior therapy, 535
- Dialysis-related amyloidosis, 213
- Diamond-Blackfan anemia, 398
- Diapedesis, 209
- Diaper rash
  - *Candida albicans*, 149
  - nystatin, 195
- Diaphoresis, 294
  - acromegaly, 333
  - serotonin syndrome, 545
- Diaphragmatic hernias, 355
- Diaphragm structures, **629**
- Diaphysis, 438
- Diarrhea
  - amebiasis, 151
  - *Bacillus cereus*, 134
  - B-complex deficiency, 61
  - bismuth/sucralfate for, 382
  - bronchial carcinoid tumor, 647
  - *Campylobacter jejuni*, 140
  - Celiac disease, 657
  - cholera toxin, 128
  - cholinesterase inhibitor poisoning, 232
  - clindamycin, 188
  - *Clostridium difficile*, 134, 652
  - *Cryptosporidium*, 151
  - as drug reaction, 240
  - ezetimibe, 306
  - giardiasis, 151
  - graft-versus-host disease, 115
  - HIV-positive adults, 173
  - hyperthyroidism and, 327
  - inflammatory bowel diseases, 365
  - irritable bowel syndrome, 366
  - lactase deficiency, 77
  - lactose intolerance, 364
  - leflunomide, 456
  - loperamide for, 382
  - magnesium deficiency from, 320
  - magnesium hydroxide, 382
  - malabsorption syndromes, 364
  - metabolic acidosis from, 561
  - metoclopramide, 383
  - misoprostol, 382
  - opioids for, 520
  - opioid withdrawal, 540
  - organisms causing, **175**
  - pellagra, 63
  - rotavirus, 164
  - *Salmonella*, 141
  - SCID, 113
  - serotonin syndrome, 545
  - *Shigella*, 141
  - threadworms, 155
  - thyroid storm and, 329
  - *Vibrio cholerae*, 141
  - VIPomas, 356
  - vitamin C toxicity, 65
  - Whipple disease, 656
  - *Yersinia enterocolitica*, 141
- Diastole
  - cardiac cycle, 276
  - coronary blood flow, 271
  - heart failure and, 298
  - heart murmurs of, 278, 279
  - heart sounds of, 276, 278
  - increased heart rate and, 272
- Diastolic pressure, 272
- Diazepam, 515
  - alcohol withdrawal, 542
  - flumazenil and, 228
  - tetanus, 134
- Diclofenac, 456
  - arachidonic acid pathway and, 455
- Dicloxacillin
  - mechanism and use, 184
  - mechanism (diagram), 183
- Dicrotic notch, 276
- Dicyclomine, 233
- Didanosine
  - HIV therapy, 199
  - mechanism (diagram), 197
  - pancreatitis, 240
- Diencephalon, 460
- Diethylcarbamazine
  - antihelminthic, 196
  - nematode infections, 155
- Diethylstilbestrol (DES), 621
  - teratogenicity, 582
  - vaginal tumors, 609
- Differential media, 122
- Differentiation (tumor), 214
- Diffuse cortical necrosis, **570**
- Diffuse glomerular disorders, 563
- Diffuse large B-cell lymphoma (DLBCL), 408, 410
- Diffuse proliferative glomerulonephritis (DPGN), 564, 661
- Diffuse scleroderma, 446
- Diffuse stomach cancer, 362
- Diffuse systemic scleroderma, 657
- Diffusion-limited gas exchange, 633
- Digestion
  - malabsorption syndromes, 364
  - secretory products for, **357–359**
  - ulcerative colitis and, 365
- Digestive tract
  - anatomy and histology, **347**
  - ligaments of, **357**
- Digitalis
  - contractility effects, 273
  - hyperkalemia and, 560
  - toxicity treatment for, 239
- Digitoxin, 45
- Digoxin, 307
  - antidote for, 118
  - for dilated cardiomyopathy, 297
  - sodium-potassium pump inhibition, 45
  - therapeutic index value of, 228
- Digoxin immune Fab, 118
- Digoxin poisoning, 310
- Dihydroergotamine, 488
- Dihydrofolate reductase, 33
- Dihydrofolic acid, 190
- Dihydroorotate dehydrogenase
  - leflunomide effect on, 33, 456
- Dihydropyridine calcium channel blockers, 244
- Dihydropyridine receptor, 433
- Dihydrorhodamine test, 113
- Dihydrotestosterone (DHT)
  - finasteride, 623
  - 5α-reductase deficiency, 604
  - function, 600
  - genital development, 590
  - pharmacologic control of, 620
  - sexual determination, 589
- Dihydroxyacetone-P, 76
- Dilated cardiomyopathy, 297, 298
  - doxorubicin, 418
  - as drug reaction, 239
  - hemochromatosis, 378
  - muscular dystrophy, 57
  - wet beriberi, 62
- Diltiazem, 304, 310
- Dimenhydrinate, **648**
- Dimercaprol
  - for arsenic toxicity, 239
  - for lead poisoning, 239, 397
  - for mercury poisoning, 239
- Dinitrophenol, 74
- Dipalmitoylphosphatidylcholine, 627
- Diphenhydramine, **648**
- Diphenoxylate, 520
- Diphtheria
  - *Corynebacterium diptheriae*, **135**
  - exotoxins, 126, 127, 128
  - unvaccinated children, 182
  - vaccine for, 135
- *Diphyllobothrium latum*
  - B_{12} deficiency, 398
  - disease association, 157
  - presentation, 156
  - vitamin B_{12} deficiency, 65
- Diplococci, 137
- Diplopia
  - drug side effects, 514
  - myasthenia gravis, 445
  - osmotic demyelination syndrome, 492
  - pseudotumor cerebri, 491
  - vertigo with, 503
- Dipyridamole, **415**
  - for coronary steal syndrome, 293
- Direct Coombs test, 108
- Direct factor Xa inhibitors, **415**
- Direct hernias, 354
- Direct inguinal hernias, 355
- Direct thrombin inhibitors, **413**
- Disc herniation, 432
- Discounted fee-for-service, 260
- Disease prevention, **259**
- Disease vectors
  - *Aedes* mosquitoes, 164
  - *Anopheles* mosquito, 153
  - armadillos, 144
  - birds, 144, 146
  - black flies, 155
  - cats, 144
  - dogs, 140, 144
  - fleas, 144, 145
  - flies, 141, 144
  - horse flies, 155
  - *Ixodes* ticks, 142
  - rodents, 163
  - ticks, 142, 145
  - zoonotic bacteria, **144**
- Disinfection/sterilization methods, 200
- Disopyramide, 308
- Disorganized speech, 530
- Disorganized thought, 529

- Dispersion measures, 251
- Displacement, 524
- Disseminated candidiasis, 149
- Disseminated intravascular coagulation (DIC), **406**
  - acute myelogenous leukemia, 410
  - amniotic fluid emboli, 637
  - Ebola, 167
  - endotoxins, 127, 129
  - meningococci, 138
  - microangiopathic anemia, 401
  - placental abruption, 606
  - schistocytes in, 395
  - Waterhouse-Friderichsen syndrome, 324, 652
- Dissociation, 524
- Dissociative amnesia, 528
- Dissociative disorders, **528**
- Dissociative fugue, 528
- Dissociative identity disorder, 528
- Distal convoluted tubules, 550
  - defects in, 556
  - diuretics and, 574
  - filtration, 553
  - nephron physiology, 555
  - renal tubular acidosis of, 562
- Distal humerus, 432
- Distal interphalangeal (DIP) joints, 429
- Distortions of hand, **429**
- Distribution, statistical, 251
- Distributive shock, 299
- Disulfiram
  - alcoholism, 661
  - alcoholism treatment, 541
  - ethanol metabolism and, 68
- Disulfiram-like reaction, 242
- Diuresis
  - atrial naturiuretic peptide, 285
  - for shock, 299
- Diuretics
  - acute interstitial nephritis with, 572
  - dilated cardiomyopathy, 297
  - electrolyte changes, **576**
  - for glaucoma, 521
  - in gout, 457
  - heart failure, 298
  - hypertension treatment, 304
  - magnesium levels and, 320
  - pancreatitis, 240
  - for SIADH, 334
  - site of action, **574**
- Diverticula, **366**, 668
- Diverticulitis, 366
- Diverticulosis, 366
- Diverticulum, 366
- Dizziness, 503
  - calcium channel blockers, 304
  - cholesteatoma, 503
  - drug side effects, 516, 518
  - nitrates, 305
  - ranolazine, 305
- *DMPK* gene, 57
- DNA
  - cloning methods, 51
  - free radical effect on, 210
  - introns vs exons, **39**
  - laddering in apoptosis, 204
  - methylation of, **32**
  - mutations in, **36**
  - repair of, **37**
  - replication of, **35**
- DNA ligase, **35**
- DNA polymerase inhibitors, 244
- DNA polymerases, **35**
- DNA topoisomerases, **35**
- DNA viruses, **160**
  - characteristics, **159**
  - genomes, **158**
  - replication, 159
- Dobutamine, 234
- Docusate, 383
- Dofetilide, 309
- Dogs (disease vectors), 140, 144, 148, 156, 176, 182
- Dominant inheritance, 55
- Dominant negative mutations, 52
- Dominant parietal cortex lesions, 481
- Donepezil, 232
  - for Alzheimer disease, 518
- Do not resuscitate order, 255
- DOPA
  - tyrosine catabolism, 79
- Dopamine, 234, 315
  - agonists, 517
  - atypical antipsychotic effects, 543
  - basal ganglia, 470
  - bupropion effect, 546
  - changes with disease, 465
  - derivation of, 79
  - Huntington disease, 490
  - kidney functions, 559
  - lactation and, 316
  - L-DOPA, 518
  - MAO inhibition, 518
  - MAO inhibitor effects, 546
  - in noradrenergic drugs, 231
  - Parkinson disease, **517**
  - pheochromocytoma secretion, 326
  - receptors, 470
  - vitamin B_6 and, 63
- Dopamine agonists
  - prolactin and, 316
  - prolactinomas, 332
- Dopamine antagonists, 316
- Dopamine receptors, 230
- Dopaminergic pathways, **468**
- Doripenem
  - carbapenems, **186**
  - mechanism (diagram), 183
- Dornase alfa (DNAse), 56
- Dorsal column of spinal cord, 478, 479
- Dorsal interossei muscle, 429
- Dorsal motor nucleus, 477
- Dorsal optic radiation, 511
- Dorsal pancreatic bud, 345
- Dosage calculations, **225**
- Double-blinded studies, 246
- "Double bubble" sign (X-ray), 344
- Double stranded viruses, 159
- Double Y males, 603
- Down syndrome, **59**
  - ALL and AML in, 410
  - cardiac defect association, 290
  - cataracts and, 505
  - chromosome associated with, 60
  - duodenal atresia and, 344
  - hCG in, 598
  - Hirschsprung disease and, 367
  - horseshoe kidney and, 549
  - presentation, 656
- Doxazosin, 236
- Doxepin, 545
- Doxorubicin, 418
  - cardiomyopathy from, 297
  - dilated cardiomyopathy, 239
  - targets, 416
  - toxicities, 422
- Doxycycline
  - chlamydiae, 146
  - *Chlamydia trachomatis*, 661
  - gonococci, 138
  - lymphogranuloma venereum, 146
  - mechanism (diagram), 183
  - MRSA, 194
  - *Mycoplasma pneumoniae*, 146
  - rickettsial/vector-borne disease, **145**
  - tetracyclines, **188**
- *DPC4/SMAD4* gene, 218
- DPP-4 inhibitors, 341
- Dressler syndrome, 294, 296, 300
  - presentation, 652
- DRESS syndrome, 514
- Drooling treatment, 233
- Drug/chemical toxicity, 210
- Drug clearance, 669
- Drug-induced lupus, 111
- Drugs
  - autonomic, **231**
  - cholinomimetic agents, 232
  - dosage calculations, 225
  - efficacy vs potency, **227**
  - elimination of, 226
  - errors in, 262
  - interactions, 225
  - metabolism of, **226**
  - patient difficulty with, 256
  - reactions to, **239–242**
  - therapeutic index, **228**
  - toxic dose, 228
  - toxicities, **239**
- Drug trials, **246**
- Dry beriberi, 62
- Dry cough with ACE inhibitors, 242
- Dry mouth
  - Lambert-Eaton myasthenic syndrome, 445
  - tricyclic antidepressants, 545
- Dry skin, 62
- Dubin-Johnson syndrome, 376, 377
- Duchenne muscular dystrophy, **57**
  - frameshift mutation, 36
  - inheritance, 56
- Ductal adenocarcinomas, 353
- Ductal carcinoma in situ (DCIS), 616
- Ductal carcinomas
  - malignant, 616
  - terminal lobular unit, 614
- Ductus arteriosus, 270, 586
- Ductus deferens
  - embryology, 589
  - ureter and, 550
- Ductus venosus, 270
- Duloxetine, 545
- Duodenal atresia, **344**
  - Down syndome, 59
- Duodenal ulcers, 363
- Duodenum
  - biliary structures and, 353
  - histology of, 347
  - location, 345
  - secretory cells, 357
- Duplex collecting system, **549**
- Dural venous sinuses, **473**
- Duret hemorrhage, 499
- Dwarfism, 333
  - achondroplasia, 435
- D-xylose test, 364
- Dynein, 44
- Dynein motors, 167
- Dysarthria, 486
  - cerebellar vermis lesions, 481
  - Friedreich ataxia as, 501
  - osmotic demyelination syndrome, 492
- Dyschezia, 613
- Dysentery
  - *Entamoeba histolytica*, 151, 175
  - *Escherichia coli*, 140
  - *Shigella* spp, **128**, 141, 175
- Dysgerminomas, 611
- Dysgeusia, 67
- Dyslipidemia, **90**
  - β-blocker adverse effects, 309
  - β-blockers, 237
  - renal failure and, 571
  - vitamin B_3 for, 63
- Dysmenorrhea
  - adenomyosis, 612
  - copper IUD, 622
  - defined, 597
  - endometriomas, 610
  - endometriosis, 613
- Dysmetria
  - stroke and, 484
  - vertigo and, 503
- Dysmyelinating diseases, **494**
- Dyspareunia, 537
  - endometriomas, 610
  - endometriosis, 613
- Dyspepsia, 623
- Dysphagia
  - esophageal pathologies and, **360–361**
  - heart enlargement and, 271
  - osmotic demyelination syndrome, 492
  - Plummer-Vinson syndrome, 396
  - stroke effects, 484
  - Zenker diverticulum, 367
- Dysplasia, 214, 215
- Dyspnea
  - aortic stenosis, 279
  - asthma, 638
  - emphysema, 655

  heart failure, 298
  hypersensitivity pneumonitis, 639
  hypertriphic cardiomyopathy, 297
  hypothyroidism and, 327
  late-onset, 638
  sudden-onset, 637
  Wegener granulomatosis, 302
Dysthymia, 530, 531
Dystonia
  benztropine for, 233
  Lesch-Nyhan syndrome, 34
  movement disorders, 489
  nigrostriatal pathway and, 468
Dystrophic calcification, 208
Dystrophin gene, 57
Dysuria, 619
  cystitis, 177
  urinary catheterization, 181
  UTIs causing, 570

E

Eardrum, 503
Early-onset Alzheimer disease, 59
Ear physiology, **503**
Eastern equine encephalitis, 163
Eating disorders, **537**
Eaton agar
  Mycoplasma pneumoniae, 146
  special culture requirements, 123
Ebola virus, 163, **167**
Ebstein anomaly, 269, 288
  fetal lithium exposure, 582
  lithium, 544
E-cadherin, 447
  in neoplastic progression, 215
Echinocandins, 194, **196**
Echinococcus granulosus
  cestodes, 156
  disease association, 157
Echinocytes, 394
Echothiophate, 521
Echovirus
  picornavirus, 163, 164
Eclampsia, 290, 608
  benzodiazepines for, 515
Ecthyma gangrenosum, 139
Ectocervix, 592
Ectoderm
  branchial clefts, 586
  derivatives of, 581
Ectoparasites, **157**
Ectopic pregnancy, **607**
  appendicitis vs, 366
  Chlamydia trachomatis, 146
  hCG in, 598
  Kartagener syndrome, 45
  methotrexate for, 417
  salpingitis and, 181
Eculizumab, 118
  for paroxysmal nocturnal hemoglobinuria, 400
Eczema
  atopic dermatitis, 449
  hyper-IgE syndrome, 112, 655
  phenylketonuria, 80
  skin scales in, 447
  type I hypersensitivity, 108
  Wiskott-Aldrich syndrome, 113, 660
Eczematous dermatitis, 448
Edema
  acute poststreptococcal glomerulonephritis, 564
  Arthus reaction, 109
  calcium channel blockers as cause, 304
  capillary fluid exchange and, 287
  cirrhosis, 372
  danazol, 622
  diabetic ketoacidosis, 337
  endotoxins, 129
  fludrocortisone, 342
  glitazone/thiazolidinediones, 340
  glomerular filtration barrier and, 551
  heart failure as cause, 298
  hyperammonia, 78
  immunosuppressants, 116
  inhalational injury, 640
  Kawasaki disease as cause, 302
  kwashiorkor, 67
  loop diuretics for, 575
  nephrotic syndrome, 566, 655
  pepripheral, 298
  periorbital, 155, 157, 327
  pitting, 298
  pseudoepherine/phenylephrine, 648
  pulmonary, 110, 575
  pulmonary hypertension, 633
  Trichinella spiralis, 155, 157
  trichinosis, 155
  wet beriberi, 62
Edema toxin, 128
Edinger-Westphal nuclei, 509
EDRF. *See* Endothelium-derived relaxing factor (EDRF)
Edrophonium, 232, 520
Edwards syndrome, **59**
  cataracts and, 505
  chromosome association, 60
  hCG in, 598
  horseshoe kidney and, 549
Efavirenz
  HIV-positive adults, 199
  mechanism (diagram), 197
Effective refractory period
  Class IA antiarrhythmic effect, 308
  Class IC antiarrhythmic effect, 308
  myocardial action potential, 280
Effective renal plasma flow, **552**, 670
Effects analysis for medical errors, 262
Efferent/afferent nerves, 285
Efferent arteriole, 550
  angiotensin II, 559
  ANP/BNP, 558
  constriction of, 553
  dopamine and, 559
  filtration, 553
Efficacy vs potency of drugs, 227
EGF. *See* Epidermal growth factor (EGF)
EGFR gene, 647
Ego defenses, **524**, **525**
EHEC, **140**
Ehlers-Danlos syndrome, **47**
  collagen deficiency in, 46
  heart murmur with, 279
Ehrlichia chaffeensis, 144
Ehrlichiosis
  animal transmission, 144
  rickettsial/vector-borne, **145**
Eikenella spp, 299
Eisenmenger syndrome, 289
Ejaculation
  innervation of, 593
  sperm pathway in, 593
Ejaculatory ducts, 593
  embryology of, 589
Ejection fraction, 273, 669
Ejection murmur, 656
Elastase, 358
  emphysema, 638
Elastic recoil, 631
Elastin, **48**
Elbow injuries, **426**
Electrocardiograms (ECGs), **282**
  acute pericarditis on, 300
  cardiac tamponade on, 300
  MI diagnosis with, 295
  tracings of, **284**
Electroconvulsive therapy, **532**
  major depressive disorder, 531
  postpartum psychosis, 532
Electroencephalogram (EEG)
  Creutzfeldt-Jakob disease, 491
  sleep stages, 467
Electrolyte disturbances, **560**
Electron transport chain, **74**
Electron transport inhibitors, 74
Elek test, 135
Elementary bodies (chlamydiae), 146
Elephantiasis, 155
11β-hydroxylase, 318
11β-hydroxysteroid dehydrogenase, 556
11-deoxycorticosterone, 318
11-deoxycortisol, 318
  metyrapone and, 324
Elfin facies, 60
Elimination of drugs, **226**
  urine pH and, 226
ELISA (enzyme-linked immunosorbent assay), **51**
  HIV diagnosis, 171
Elliptocytes, 394
Elliptocytosis, 394
Elongation of protein synthesis, 41
Eltrombopag, 117
Emancipated minors, 254
EMB agar
  Escherichia coli, 177
  lactose-fermenting enterics, 138
  special culture, 123
Emboli
  atherosclerosis, 292
  atrial fibrillation, 284
  atrial septal defect, 289
  bacterial endocarditis, 299
  patent foramen ovale, 268
  pulmonary, 299
Embolic stroke, 482
Emboliform nucleus, 469
Embolism
  pulmonary, 561
Embryogenesis
  genes involved in, **580**
  intrinsic pathway and, 204
Embryology
  cardiovascular, **268–270**
  derivatives of, **581**
  erythropoiesis, 389
  gastrointestinal, 344–345
  genital, 589
  neurological, 460–462
  renal, 548–549
  reproductive, 580–591
  respiratory, 626–627
  thyroid development, 312
  USMLE Step 1 preparation, 264
Embryonal carcinomas, 618
Embryonic age calculation, 598
Embryonic morphogenic, errors, **581**
Emollient laxatives, 383
Emotionally distraught patients, 256
Empagliflozin, 341
Emphysema
  α_1-antitrypsin deficiency, 375
  compliance in, 631
  diffusion in, 633
  diffusion-limited gas exchange, 633
  elastin in, 48
  presentation, 655
Empty sella syndrome, 335
Emtricitabine
  HIV-positive adults, 199
  mechanism (diagram), 197
Enalapril, 577
Encapsulated bacteria, **124**
Encephalitis
  anti-NMDA receptor, 217
  Cryptococcus neoformans, 149
  cytomegalovirus, 173
  guanosine analogs, 197
  herpesviruses, **160**, 176
  HIV-positive adults, 173
  HSV identification, **162**
  Lassa fever, 163
  neonatal, 178
  rubeola, 166
  small cell lung cancer, 647
  togaviruses, 163
  West Nile virus, 176
Encephalopathy
  hepatic, 374
  hypertensive emergency, 290
  lead poisoning, 397
  Lyme disease, 142
  mitochondrial, 55
  prion disease, 174
  renal failure, 571
  Reye syndrome, 373
  Wernicke, 62
End-diastolic volume, 272
Endemic typhus, 144
Endocannabinoids, 317
Endocardial cushion, 268
Endocardial fibroelastosis, 297

- Endocarditis
  - bacterial, **299**
  - *Candida albicans*, 149
  - coarctation of aorta, 289
  - *Coxiella burnetii*, 145
  - daptomycin, 191
  - enterococci, 133
  - heart murmurs, 279
  - heroin addiction and, 541
  - nonbacterial thrombotic, 217
  - prophylaxis, 194
  - *Staphylococcus aureus*, 131
  - *Streptococcus bovis*, 133
  - viridans streptococci, 125, 132
- Endocervix, 592
- Endochondrial ossification, 434
- Endocrinal drug reactions, **240**
- Endocrinal paraneoplastic syndromes, 217
- Endocrine hormone signaling pathways, **322**
- Endocrine pancreas cell types, **313**
- Endocrine system, **312–342**
  - anatomy, 312–313
  - embryology, 312
  - pathology, 323–339
  - pharmacology, 340–342
  - physiology, 314–322
- Endoderm
  - branchial pouch derivation, 586
  - derivatives of, 581
- Endodermal tubules, 626
- Endometrial artery, 584
- Endometrial cancer, 612
  - epidemiology of, 608
  - estrogens and, 621
  - Lynch syndrome and, 371
  - PCOS and, 609
  - progestins for, 622
  - tamoxifen and, 421
  - tumor suppressor genes and, 218
- Endometrial hyperplasia, 612
  - follicular cysts, 610
  - progesterone and, 595
- Endometrial vein, 584
- Endometriomas, 610
- Endometriosis, 613
  - danazol for, 622
  - endometriomas and, 610
  - ovarian neoplasms and, 610
- Endometritis, 612
  - pelvic inflammatory disease, 181
- Endometrium, 592
  - conditions of, **612**
- Endoneurium, 465
- Endoplasmic reticulum, 42, 43
- Endosomes, 43
- Endothelial cells
  - filtration and, 553
  - glomerulus, 550
  - leukocyte extravasation and, 209
  - in wound healing, 211
- Endothelium-derived relaxing factor (EDRF), 322
- Endotoxins, **127**, **129**
- End-stage renal disease findings, 661
- End-systolic volume, 272
- Enflurane, 519
  - seizures with, 242
- Enfuvirtide
  - HIV-positive adults, 199
  - mechanism (diagram), 197
- Enhancers (gene expression), **38**
- Enoxacin, 191
- Enoxaparin, 413
  - deep venous thrombosis, 636
- Entacapone, 517
- *Entamoeba histolytica*
  - amebiasis, **151**
  - bloody diarrhea, 175
  - metronidazole, 191
- Enteritis
  - vitamin B_5 deficiency, 63
  - vitamin B_7 deficiency, 64
  - vitamin B_{12} deficiency, 65
- *Enterobacter* spp
  - lactose fermentation, 138
  - nosocomial infection, 181
  - taxonomy, 121
- *Enterobacter aerogenes*, 185
- *Enterobius* spp
  - diseases association, 157
  - infection routes, 154
- *Enterobius vermicularis*, 155
- Enterochromaffin-like cells, 325
- Enterococci, **133**
  - penicillins for, 184
  - vancomycin, 186
  - vancomycin-resistant (VRE), 133
- *Enterococcus* spp
  - Gram-positive algorithm, 130
  - UTIs, 177
- *Enterococcus faecalis*, 133
- *Enterococcus faecium*, 133
- Enterohemorrhagic *Escherichia coli* (EHEC), 128, **140**, 175
- Enterohemorrhagic *Escherichia coli* (EHEC)
  - hemolytic-uremic syndrome, 405
- Enteroinvasive *Escherichia coli* (EIEC), 140, 175
- Enterokinase/enteropeptidase, 358
- Enterotoxigenic *Escherichia coli* (ETEC), 128, 140, 175
- Enterovirus meningitis, 176
- Enveloped viruses, 158
- Envelopes (viral), **159**
- *env* gene, 171
- Enzyme kinetics, **224**
  - antagonists, 228
  - partial agonists, 228
- Enzymes
  - rate-determining, 69
  - terminology for, **69**
- Eosinopenias, 402
- Eosinophilia, 387
  - *Aspergillus fumigatus*, 149
  - *Chlamydia trachomatis*, 146
  - macrolides, 189
- Eosinophilic casts, 570
- Eosinophilic esophagitis, 360
- Eosinophils, **387**
  - corticosteroid effects, 402
  - in esophagus, 360
  - helminths, 154
- Ependymoma, 498
- Ephedrine, 234
  - as noradrenergic drug, 231
- Epicanthal folds
  - cri-du-chat syndrome, 60
  - Down syndrome, 59
- Epidemics, 165
- Epidemic typhus, 144
- Epidemiology/biostatistics, **246–252**
- Epidermal growth factor (EGF)
  - signaling pathways for, 322
  - in wound healing, 211
- Epidermis, 446
  - embryologic derivatives, 581
- *Epidermophyton*, 148
- Epididymis, 593
  - embryology of, 589
- Epididymitis, 180
- Epidural hematomas, 483
- Epigastric veins, 350
- Epiglottitis
  - *Haemophilus influenzae*, 138
  - labs/findings, 660
  - unvaccinated children, 182
- Epilepsy
  - drug therapy, **514–515**
  - gustatory hallucinations in, 529
  - lung abscesses, 646
  - seizures, 487
  - splice site mutations, 36
  - Sturge-Weber syndrome, 495
- Epileptic patients
  - confidentiality exceptions, 255
- Epinephrine, 234. *See also* Catecholamines
  - adrenal medulla secretion, 312
  - α-blockade of, 236
  - for anaphylactic reaction, 110
  - for glaucoma, 521
  - glycogen regulation and, **81**
  - in nervous system, 229
  - pheochromocytoma secretion, 326
  - tyrosine catabolism, 79
  - unopposed secretion of, 336
  - vitamin B_6 and, 63
- Epineurium, 465
- Epiphyseal tumors, 438
- Epiploic foramen of Winslow, 346
- Episcleritis
  - inflammatory bowel disease, 365
- Epispadias, 591
- Epistaxis, **636**
  - hereditary hemorrhagic telangiectasia, 303
  - Osler-Weber-Rendu syndrome, 656
- Epithelial cell junctions, **447**
- Epithelial cells
  - tumor nomenclature of, 216
- Epithelial hyperplasia, 615
- Epithelial tumors, 44
- Epithelium, 347
- Eplerenone, 576
- Epoietin alfa, 117
- Epoprostenol
  - pulmonary hypertension, 648
- Epstein-Barr virus (EBV), 161
  - aplastic anemia, 399
  - Burkitt lymphoma, 408
  - false-positive VDRL, 143
  - hairy leukoplakia and, 451
  - head and neck cancer, 636
  - HIV-positive adults, 173
  - Hodgkin lymphoma, 407
  - in immunodeficient patients, 114
  - labs/findings, 657, 660
  - oncogenesis of, 219
  - receptors for, 162
- Eptifibatide, 415
  - thrombogenesis and, 393
- Erb palsy, 428
- Erectile dysfunction, 537
  - β-blockers and, 237, 309
  - cimetidine, 381
  - Lambert-Eaton myasthenic syndrome, 445
  - PDE-5 inhibitors for, 623
  - Peyronie disease, 617
  - sildenafil, 648
- Erection
  - autonomic innervation, 593
  - ischemic priapism, 617
- Ergosterol synthesis, 194
- Ergosterol synthesis inhibitors, 244
- Ergot alkaloids, 239
- Eriotinib, **420**
- Errors (medical), 262
- Ertapenem, 183, 186
- Erysipelas, 451
  - *Streptococcus pyogenes*, 132
- Erythema
  - complicated hernias, 355
  - Kawasaki disease, 302
- Erythema marginatum, 132, 300
- Erythema migrans, 142
- Erythema multiforme, 452
- Erythema nodosum, 147, 444, 453
  - inflammatory bowel disease, 365
- Erythroblastosis fetalis, 390
  - type II hypersensitivity, 108
- Erythrocytes, **386**
  - blood types, 390
  - casts in urine, 562
  - Coombs test, 401
  - DAF deficiency and, 103
  - erythropoietin and, 559
  - glucose usage by, 314
  - hereditary spherocytosis, 400
  - macrophages and, 387
  - multiple myeloma, 409
  - myeloproliferative disorders, 411
  - pathologic forms of, **394–395**
- Erythrocyte sedimentation rate (ESR), **212**
  - osteomyelitis, 176
  - subacute granulomatous thyroiditis, 328
- Erythrocytosis, 386
  - oxygen-hemoglobin dissociation curve, 632
- Erythromelalgia
  - essential thrombocythemia, 411
  - polycythemia vera, 411
- Erythromycin
  - diarrhea, 240
  - macrolides, 189

  mechanism (diagram), 183
  prophylaxis, 194
  protein synthesis inhibition, 187
  reactions to, 240
Erythroplasia of Queyrat, 617
Erythropoiesis, 642
Erythropoietin
  anemia of chronic disease, 399
  aplastic anemia, 399
  high altitude, 635
  polycythemia and, 217, 652
  polycythemia vera, 411
  release of, 559
  signaling pathways for, 322
Escherichia coli, **140**
  catalase-positive organism, 124
  cephalosporins, 185
  culture requirements, 123
  EMB agar, 138
  encapsulation, 124
  galactosemia as cause, 76
  Gram-negative algorithm, 137
  immunodeficiency infections, 114
  lactose fermentation, 138
  meningitis, 176, 664
  neonatal illness, 178
  nosocomial infection, 181
  penicillins for, 184
  pneumonia, 175
  prostatitis, 619
  splenic dysfunction and, 94
  taxonomy, 121
  type III secretion system, 125
  urinary tract infections, 570, 668
  UTIs, 177
Escherichia coli O157:H7, 128, 140, 174, 175
E-selectin, 209
Esmolol, 237, 309
Esomeprazole, 381
Esophageal atresia, 344
Esophageal cancer, **361**
  achalasia and, 360
Esophageal dysmotility
  CREST syndrome, 446
Esophageal squamous cell carcinomas, 360
Esophageal strictures, 360
Esophageal varices, 350, 360
Esophageal veins, 350
Esophageal webs, 360, 396
Esophagitis, 360
  bisphosphonates, 456
  as drug reaction, 240
  HIV-positive adults, 173
Esophagus
  blood supply and innervation, 348
  diaphragm, 629
  histology of, 347
  pathologies of, **360**
  portosystemic anastomosis, 350
Essential amino acids, 77
Essential fructosuria, 76
Essential hypertension, 304
Essential mixed cryoglobulinemia, 169
Essential thrombocythemia, 411
Essential tremor, 489
Esters as local anesthetics, 519
Estradiol, 620
Estriol
  Down syndrome, 59
  pharmacologic control, 620
Estrogen, **595**, **621**
  androgen insensitivity syndrome, 604
  benign breast tumors, 615
  bone formation, 434
  breast cancer, 616
  contraception and, 622
  endometrial carcinoma, 612
  epiphyseal plate closure, 600
  in genital development, 590
  Granulosa cell tumors, 611
  gynecomastia, 615
  Klinefelter syndrome, 603
  lactation and, 599
  leiomyomata, 612
  menopause, 600
  menstrual cycle, 597
  osteoporosis, 435
  ovulation, 596
  pregnancy, 598
  premature ovarian failure, 609
  progesterone and, 595
  prolactin suppression of, 316
  signaling pathways for, 322
  thecoma, 610
  Turner syndrome, 603
Estrone, 620
Eszopiclone, 515
Etanercept, 457
  lupus-like syndrome, 241
Ethacrynic acid, **575**
Ethambutol, 192, **193**
Ethanol
  as carcinogen, 219
  metabolism, **68**
  zero-order elimination of, 226
Ethics, **253–256**
  confidentiality, **255**
  consent, 254
  core principles of, **253–255**
  directives, **255**
  error disclosure, 262
  religious beliefs and, 257
  situations in, **256–257**
Ethinyl estradiol, 621, 622
Ethosuxamide, 514
Ethosuximide
  absence seizures, 661
Ethylenediaminetetraacetic (EDTA), 397
Ethylene glycol
  metabolic acidosis, 561
  toxicity treatment, 239
Etonogestrel, 622
Etoposide, **419**
  in cell cycle, 416
  targets of, 416
Etoposide/teniposide, 35
Euchromatin, **32**
Eukaryotes
  DNA replication, 35
  functional gene organization, **38**
  ribosomes in, 41
  RNA processing, **38**
Eustachian tubes
  embryonic derivation, 588
Evolocumab, 306
Ewing sarcomas, 438
  dactinomycin for, 418
  labs/findings, 660
Exanthem subitum, 161
Excitatory pathway, 470
Exclusive Provider Organization, 259
Executioner caspases, 204
Exemestane, 621
Exenatide, 341
Exercise
  blood flow autoregulation, 286
  cardiac output, 272
  peripheral resistance, 275
  respiratory response, 635
  syncope with, 297
  Tetralogy of Fallot, 288
Exocrine glands, 229, 230
Exons vs introns, **39**
Exophytic mass (colorectal cancer), 371
Exotoxin A
  Pseudomonas aeruginosa, 128, 139
  Streptococcus pyogenes, 129
Exotoxins
  features of, **127**
  organisms with, 128–129
Expectorants, 648
Expiratory reserve volume (ERV), 630
External hemorrhoids, 351
External iliac arteries, 348
External iliac lymph nodes, 591
External inguinal ring, 355
External spermatic fascia, 354
Extinction (conditioning), 524
Extracellular fluid (ECF), 551
Extragonadal germ cell tumors, **618**
Extraperitoneal tissue, 354
Extravascular hemolysis, 399
Extrinsic hemolytic anemia, **401**
Extrinsic pathway, **204**
  coagulation, 391
  warfarin and, 414
Exudate pleural effusion, 644
Exudate vs transudate, **212**
Ex vacuo ventriculomegaly, 492
Eye disorders
  AIDS retinitis, 161
  aniridia, 569
  episcleritis, 365
  red-green color blindness, 193
  retinopathy, 196
  retinopathy of prematurity, 627
  scleritis, 439
  uveitis, 365
Eyes
  anatomy of, **504**
  aqueous humor pathway, 505
  bilateral movement of, 513
  cherry-red macular spot, 84
  motility of, 510
  scleral arcus, 90
Ezetimibe, 306
  diarrhea, 240

F

Fab region of antibodies, 100
Fabry disease, 84
  inheritance, 56
Facial dysmorphism, 582
Facial nerve (CN VII), **476**
  brain stem location, 474
  branchial arch derivative, 587
  lesions in, **502**
  pathway for, 476
  in tongue, 463
Facial nerve palsy, 502
  Lyme disease, 142
Facies
  abnormal, 61
  "chipmunk," 397
  dysmorphism, 581
  elfin, 60
  epicanthal folds, 59, 60
  flat, 59
  moon, 323
Factitious disorder, **536**
Factor IX concentrate, 404
Factor VIII concentrate, 404
Factor V Leiden, 406
Factor V Leiden mutation, 392
Factor Xa
  direct inhibitors of, 415
  heparin effect on, 413
Factor Xa inhibitors, 391
Factor XI concentrate, 404
Facultative intracellular organisms, 124
FADH (flavin adenine dinucleotide), 73
Failure mode analysis, 262
Failure to thrive, 526
  galactosemia, 76
  orotic aciduria, 398
  SCID, 113
Falciform ligament, 346
Fallopian tubes
  anatomy, 592
  epithelial histology, 592
  fertilization, 598
False-negative rate, 247
False-positive rate, 247
Falx cerebri, 499
Famciclovir, **197**
Familial adenomatous polyposis, 370
  APC gene and, 372
  chromosome association, 60
  labs/findings, 660
Familial dyslipidemias, **90**
Familial hypercholesterolemia, 90
  presentation, 652
Familial hypocalciuric hypercalcemia, 332
Family discussions, 256
Family therapy
  separation anxiety, 527
Famotidine, 381
Fanconi anemia, 399
  nonhomologous end joining and, 37
  presentation, 656

- Fanconi syndrome, **556**
  - drug reaction and, 242
  - presentation, 655
  - renal tubular acidosis, 562
  - Wilson disease, 378
- Fascia
  - collagen in, 46
- Fasciculations, 499
- Fastigial nucleus, 469
- Fasting plasma glucose test, 336
- Fasting state, 72, 87
- Fast twitch muscle fibers, 433
- Fat emboli, 637
- Fatigue
  - adrenal insufficiency, 324
  - adrenocortical insufficiency, 656
  - heart failure and, 298
  - hypothyroidism, 327
  - MI signs, 294
- Fat necrosis, 205, 615
- Fat redistribution, 241
- Fat-soluble vitamins, **61**
- Fatty acids
  - gluconeogenesis, 74
  - metabolism of, **85**
  - oxidation of, 68, 69
- Fatty acid synthase, 63
- Fatty acid synthesis
  - metabolic site, 68
  - rate-determining enzyme, 69
- Fatty casts, 562
  - nephrotic syndrome, 566
- Fatty liver
  - nonalcoholic, 374
  - Reye syndrome, 373
- Fatty liver disease
  - hepatocellular carcinoma and, 375
  - labs/findings, 660
- Fava beans and G6PD deficiency, 400
- Fc region of antibodies, 100
- Febrile nonhemolytic transfusion reaction, 110
- Febrile pharyngitis, 160
- Febuxostat
  - gout, 440, 457, 661
  - Lesch-Nyhan syndrome, 34
- Fecal elastase, 364
- Fecalith obstruction, 366
- Fecal microbiota transplant, 134
- Fecal retention, 528
- Feces
  - bilirubin excretion, 359
  - explosive expulsion of, 367
- Federation of State Medical Boards (FSMB), 2
- Fed state, 72, 87
- Felty syndrome, 439
- Female genital embryology, 589
- Female reproductive anatomy, **592**
- Female reproductive epithelial histology, **592**
- Femoral artery, 353
- Femoral hernias, 355
- Femoral nerve, 353, 430
- Femoral region, **353**
- Femoral ring, 353
- Femoral sheath, 353
- Femoral triangle, 353
- Femoral vein, 353
- Fenofibrate, 306
- Fenoldopam, 234, 304
- Fentanyl, 520
- Ferritin
  - acute-phase reactant, 102
  - anemia, 402
  - anemia of chronic disease, 399
  - iron deficiency anemia, 396
  - lab values in anemia, 402
  - sideroblastic anemia, 397
- Ferrochelatase, 403
- Fertility
  - double Y males, 603
  - GnRH and, 315
  - menstrual cycle, 597
- Fertilization, 596, 598
- Fetal alcohol syndrome, 290, 582, **583**
  - holoprosencephaly and, 461
- Fetal circulation, **270**
- Fetal death
  - parvovirus, 160
- Fetal development, **580**
- Fetal distress
  - placental abruption, 606
  - vasa previa, 607
- Fetal erythropoiesis, **389**
- Fetal hemorrhage, 582
- Fetal hypothyroidism, 328
- Fetal lung maturity, 627
- Fetal-postnatal derivatives, **270**
- Fetal respiration, 626
- Fetal tissue
  - collagen in, 46
- Fetor hepaticus, 372
- Fever
  - amphotericin B, 195
  - bacterial endocarditis, 299
  - childhood rashes, **179**
  - clindamycin, 188
  - complicated hernias, 355
  - endotoxins, 127
  - epiglottitis, 182
  - exotoxins, 129
  - following MI, 652
  - genital herpes, 180
  - high, 161, 164, 167, 179
  - Jarisch-Herxheimer reaction, 143
  - Legionnaires' disease, 139
  - low-grade, 139, 167, 407
  - malaria, 153
  - mononucleosis, 161
  - *Pseudomonas aeruginosa*, 139
  - pulmonary anthrax, 133
  - recurring, 152
  - *Rickettsia rickettsii*, 145
  - *Salmonella* spp, 144
  - *Salmonella typhi*, 141
  - seizures with, 161
  - Tetralogy of Fallot, 288
  - thyroid storm causing, 329
  - toxic shock syndrome, 131
  - *Trichinella spiralis*, 155
  - tuberculosis, 136
  - vasculitides, 302
  - Waterhouse-Friderichsen syndrome, 138
  - Weil disease, 142
- Fexofenadine, 648
- FGF. *See* Fibroblast growth factor
- *FGF* gene, 580
- Fibrates, 306
  - hepatitis and, 240
  - myopathy and, 241
- Fibrinogen
  - acute-phase reactant, 102
  - in cryoprecipitate, 407
  - ESR and, 212
  - platelet plug formation, 393
  - receptor for, 386
  - thrombocytes, 386
  - thrombogenesis, 393
- Fibrinoid necrosis, 205
- Fibrinolysis, 392
- Fibrinolytic system, 391
- Fibrinous pericarditis, 294
- Fibroadenomas, 614, 615
- Fibroblast growth factor (FGF)
  - signaling pathways for, 322
  - in wound healing, 211
- Fibroblast growth factor receptor (FGFR3), 435
- Fibroblasts
  - cortisol and, 319
  - Graves disease, 329
  - in wound healing, 211
- Fibrocystic breast disease, 615
- Fibroid tumors, 612
  - leuprolide for, 621
- Fibromas, 610
  - nomenclature for, 216
- Fibromuscular dysplasia, 290
- Fibromyalgia, 444
- Fibronectin
  - cryoprecipitate, 407
  - thrombocytes, 386
- Fibrosarcomas, 216
- Fibrosis
  - diffusion-limited gas exchange, 633
  - silicosis, 641
- Fibrous plaque in atherosclerosis, 292
- Fick principle, 272
- Fidaxomicin, 134
- Fifth disease
  - B19 virus, 160
  - rash, 179
- 50S inhibitors, 187
- Filgrastim, 117
- Filoviruses
  - characteristics of, 163
  - Ebola, 167
  - negative-stranded, 164
- Filtration, **553**
- Filtration fraction, 670
  - glomerular dynamics, 553
- Fimbria, 120, 592
- Financial considerations in treatment, 257
- Finasteride, 623
  - reproductive hormones and, 620
- Fingernails
  - glomus tumors under, 450
- First-order elimination, 226
- Fishbone diagram, 262
- Fishy smell, 144
- Fitz-Hugh-Curtis syndrome, 138, 181
- 5-aminosalicylic drugs, 365, 382
- 5α-reductase
  - inhibitors for BPH, 619
  - deficiency, 589, 604
  - testosterone conversion, 600
- 5α-reductase inhibitors
  - benign prostatic hyperplasia, 661
- 5-fluorouracil, 417
  - in cell cycle, 416
  - photosensitivity, 241
  - pyrimidine synthesis, 33
  - targets of, 416
  - toxicities of, 422
- 5-HT
  - MAO inhibitor effect on, 546
  - mechanism of, 544
  - opioid effects, 520
  - serotonin syndrome, 545
  - tramadol effect, 521
  - trazodone effects, 546
- 5-HT$_{1B/1D}$ agonists
  - naming convention for, 244
- 5-HT agonists, 516
- 5-hydroxyindoleacetic acid (5-HIAA)
  - in carcinoid syndrome, 338
  - neuroendocrine tumors, 325
- Fixation, 525
- Fixed splitting, 277
- Flaccid paralysis
  - botulinum toxin, 128, 134
  - LMN lesion, 501
  - motor neuron signs, 499
- Flagellin, 95
- Flagellum, 120
- Flash cards for USMLE Step 1 exam, 13
- Flat affect, 468
- Flat facies, 59
- Flavin nucleotides, 71
- Flaviviruses, 159, 163
- Fleas (disease vectors), 144, 145
- Flecainide, 308
- Flexor digiti minimi muscle, 429
- Flexor pollicis brevis muscle, 429
- Flies (disease vectors), 141, 155
- Floppy baby syndrome
  - botulinum toxin as cause, 128
  - *Clostridium botulinum* as cause, 134
  - spinal cord lesions, 500
- Flow cytometry, **50**
- Flow volume loops, **637**
- Fluconazole
  - *Candida albicans*, 661
  - mechanism and use, 195
  - mechanism (diagram), 194
  - opportunistic fungal infections, **149**
  - systemic mycoses, 147
- Flucytosine, **195**
- Fludrocortisone, **342**. *See also* Glucocorticoids

- Fluid compartments, **551**
- Flumazenil
  - benzodiazepine overdose, 239, 515, 540
  - diazepam and, 228
  - nonbenzodiazepine hypnotics, 515
- Fluorescence in situ hybridization, **51**
- Fluorescent antibody stain, 122
- Fluoroquinolones, 35
  - mechanism and use, **191**
  - mechanism (diagram), 183
  - *Mycoplasma pneumoniae*, 146
  - pregnancy contraindication, 201
  - *Pseudomonas aeruginosa*, 139
  - tendon/cartilage damage with, 241
  - typhoid fever, 141
- Fluoxetine, 545
- Fluphenazine, 543
  - Tourette syndrome, 527, 542
- Flutamide, 623
  - reproductive hormones and, 620
- Fluticasone, 649
- *FMR1* gene, 58
- Foam cells
  - in atherosclerosis, 292
  - Niemann-Pick disease, 84
- Focal glomerular disorders, 563
- Focal hepatic necrosis, 240
- Focal necrotizing vasculitis, 302
- Focal neurological deficits
  - hyperosmolar hyperglycemia nonketotic syndrome as cause, 338
  - pituitary apoplexy, 335
- Focal neurological defitics
  - pituitary adenoma, 332
- Focal segmental glomerulosclerosis, 566
- Focal seizures, 487
- Folate antagonists, 582
- Folate synthesis
  - inhibition/block, 183, 190
- Folic acid
  - antimicrobials and, 183
  - neural tube defects and, 461
  - in pregnancy, 64
- Follicles (lymph), 92
- Follicle-stimulating hormone (FSH)
  - clomiphene effect, 621
  - cryptorchidism, 617
  - hCG and, 598, 618
  - Kallmann syndrome, 604
  - Klinefelter syndrome, 603
  - leuprolide, 621
  - menopause, 600
  - ovulation/spermatogenesis and, 316
  - PCOS, 609
  - pharmacologic control of, 620
  - premature ovarian failure, 609
  - progesterone and, 595
  - secretion of, 313
  - signaling pathways of, 322
  - spermatogenesis, 594
  - Turner syndrome, 603
- Follicular conjunctivitis, 146
- Follicular cysts, 610
- Follicular lumen, 321
- Follicular lymphoma, 412
- Follicular lymphomas, 204, 408, 668
  - chromosomal translocations and, 412
- Follicular phase, 597
- Follicular phase of menstrual cycle, 597
- Follicular thyroid carcinomas, 330
- Fomepizole
  - ethanol metabolism and, 68
  - toxicity treatment with, 239
- Fondaparinux, 391
- Food allergies and eczema, 449
- Food poisoning
  - *Bacillus cereus*, 134
  - causes of, 127, 174
  - *Staphylococcus aureus*, 131
  - toxic shock syndrome toxin, 129
- Food toxins, **238**
- Foot drop
  - lead poisoning, 397
- Foramen cecum, 312
- Foramen magnum, 476
- Foramen of Magendie, 474
- Foramen of Monro, 474
- Foramen ovale
  - atrial septal defect, 289
  - embryology, 268
  - fetal circulation, 270
  - retained patency of, 288
- Foramen ovale (skull), 476
- Foramen primum, 268
- Foramen rotundum, 476
- Foramen secundum, 268
- Foramen spinosum, 476
- Foramina of Luschka, 474
- Forebrain, 460
- Foregut
  - blood supply/innervation of, 348
  - development of, 344
- Formoterol, 649
- Fornix, 468
- Fornix (uterus), 592
- 46,XX/46,XY DSD, 604
- Fosamprenavir
  - HIV-positive adults, 199
  - mechanism (diagram), 197
- Foscarnet, **198**
- Fosphenytoin, 514
- Fossa ovalis, 270
- Fovea, 504
  - cherry-red spot, 507
- FOXP3 protein, 98
- Fragile X syndrome, **58**
  - chromosome association, 60
  - dominant, inheritance of, 55
- Frameshift mutations, **36**
  - muscular dystrophy and, 57
- *Francisella* spp
  - intracellular organism, 124
  - taxonomy, 121
- *Francisella tularensis*
  - animal transmission, 144
  - Gram-negative algorithm, 137
- Frataxin, 501
- Free fatty acids
  - diabetic ketoacidosis and, 337
  - fast/starvation states, 87
  - lipid transport and, 88
- Free nerve endings, 464
- Free radical injury, 207, **210**
- Fresh frozen plasma, 407
  - warfarin reversal, 664
  - for warfarin toxicity, 239
- "Fried egg" cells, 611
- Friedreich ataxia, **501**
  - chromosome association, 60
  - hypertrophic cardiomyopathy, 297
- Frontal eye fields
  - cortical functions, 471
  - lesions in, 481
- Frontal lobe
  - lesions in, 481
  - stroke effects, 484
- Frontotemporal dementia, 490, 492
- Fructokinase, 76
- Fructose-1,6-bisphosphatase, 69
  - gluconeogenesis, 74
  - in metabolic pathways, 70
- Fructose-2,6-bisphosphate, **72**
- Fructose intolerance, 76
- Fructose metabolism
  - disorders, 76
  - pathways, 70
- Fructosuria, 76
- FSH. *See* Follicle-stimulating hormone
- FTA-ABS test, 143
- Fumarate, 78
- Functional residual capacity (FRC), 630
  - chest wall and, 631
  - in flow volume loops, 637
- Fundus, 592
- Fungal infections
  - IL-12 receptor deficiency, 112
  - thymic aplasia, 112
- Fungi
  - culture requirements, 123
  - immunocompromised patients, 175
  - necrosis and, 205
  - opportunistic infections, 149
  - silver stain, 122
  - topical infections, 195
- Funny current, 281, 310
- Furosemide, 243, **575**
  - gout with, 241
  - interstitial nephritis, 242
  - pancreatitis, 240
- Fusion inhibitors, 199
- *Fusobacterium* spp
  - alcoholism, 175
  - anaerobic metabolism, 123
  - lung abscesses, 646

G

- G6PD
  - deficiency, 56, **75**
  - HMP shunt and, 69
  - in respiratory burst, 105
- G6PD deficiency, 400
  - in anemia taxonomy, 396
  - degmacytes in, 394
  - Heinz bodies in, 395
- GABA, 465
  - barbiturate effects, 515
  - basal ganglia and, 470
  - benzodiazepine effect, 515
  - changes with disease, 465
  - derivation of, 79
  - epilepsy drugs, 514
  - Huntington disease, 490
  - vitamin B_6 and, 63
- GABA channels, 196
- Gabapentin, 514
- $GABA_B$ receptor agonists, 493
- *gag* gene, 171
- Gag reflex, 477
- Gait disturbance
  - muscular dystrophy, 57
- Gait disturbances
  - Parkinson disease, 655
- Galactocerebrosidase, 84
  - Krabbe disease, 494
- Galactocerebroside, 84
- Galactokinase, 70
- Galactokinase deficiency, 76
  - cataracts and, 505
- Galactorrhea
  - antipsychotic drugs and, 315
  - pituitary prolactinomas, 315
  - tuberoinfundibular pathway, 468
- Galactose-1-phosphate, 70
- Galactose-1-phosphate uridyltransferase, 76
- Galactose metabolism
  - diagram, 70
  - disorders of, **76**
- Galactosemia, 76
  - cataracts and, 505
- Galantamine
  - for Alzheimer disease, 518
- Galant reflex, 480
- Gallbladder
  - biliary structures, 353
  - blood supply and innervation of, 348
  - regulatory substances, 356
- Gallbladder cancer
  - porcelain gallbladder and, 379
  - sclerosing cholangitis and, 378
- Gallstone ileus, 379
- Gallstones. *See* Cholelithiasis
- γ-glutamyltransferase (GGT)
  - alcohol use, 540
- γ-glutamyl transpeptidase (GGT), 373
- γ-interferon, 387
- Ganciclovir, **198**
  - agranulocytosis, 241
- Ganglioneuromatosis, 656
- Gangrene
  - Buerger disease, 302
  - diabetes mellitus, 336
- Gangrenous necrosis, 205
- Gap junctions, 447
- Gardener's pupil, 233
- *Gardnerella* spp, 121

Gardnerella vaginalis, **144**
  labs/findings, 660
Gardner syndrome, 370
Gargoylism, 84
Garlic breath, 72
Gas gangrene
  alpha toxin, 129
  Clostridium perfringens, 127, 134, 175
Gastrectomy, 398
Gastric acid, **357**
  histamine receptors and, 230
  regulatory substances and, 356
Gastric adenocarcinomas
  acanthosis nigricans and, 453
  Helicobacter pylori, 142
Gastric arteries
  celiac trunk, 349
  intraligmental, 346
Gastric bypass surgery
  ghrelin and, 356
  vitamin B$_{12}$ deficiency, 65
Gastric cancer, **362**
  carcinogens causing, 219
  metastases of, 221
  oncogenes and, 218
  oncogenic microbes and, 219
  sign of Leser-Trélat and, 217
  trastuzumab for, 421
Gastric obstruction, 363
Gastric sclerosis, 446
Gastric ulcers, 363
  NSAID toxicity, 456
Gastric vessels, 346
Gastrin, 356, 357
  signaling pathways for, 322
  somatostatinomas and, 338
Gastrinomas, 342
Gastritis, **362**
  associations, 664
  gastrin in, 356
  H$_2$ blockers for, 381
  Helicobacter pylori, 142
  proton pump inhibitors for, 381
  stomach cancer and, 362
Gastrocolic ligament, 346
Gastroduodenal artery, 349
Gastroenteritis
  calciviruses, 163
  Listeria monocytogenes, 135
  rotavirus, 164
  Salmonella spp, 141
Gastroepiploic arteries, 346, 349
Gastroesophageal reflux disease
  esophageal cancer and, 361
  presentation, 360
Gastrohepatic ligament, 346
Gastrointestinal bleeding
  hereditary hemorrhagic telangiectasia, 303
  iron poisoning, 404
  Osler-Weber-Rendu syndrome, 656
Gastrointestinal drug reactions, **240**
Gastrointestinal ligaments, **346**
Gastrointestinal stromal tumors (GISTs), 218
Gastrointestinal system, **344–383**
  anatomy, 345–354
  blood supply to, **348**
  embryology, 344–345
  innervation of, **348**
  pathology, 359–380
  pharmacology, 381–383
  physiology, 356–360
  regulatory substances, **356**
  secretory products, **357**
Gastroschisis, 344
Gastrosplenic ligament, 346
Gaucher disease, 84
  osteonecrosis, 436
Gaussian distribution, 251
G-CSF. *See* Granulocyte-colony stimulating factor (G-CSF)
Gel electrophoresis, 48
Gemfibrozil, 306
Gemifloxacin, 191
Gender dysphoria, **537**
Gender identity, 258
Gene expression
  modifications, **52**
  regulation, **38**
Gene inheritance modes, 55
General anesthetic, 244
Generalized anxiety disorder (GAD), 532, **533**
  buspirone, 544
  drug therapy for, 542
  Selective serotonin reuptake inhibitors (SSRIs) for, 545
  serotonin-norepinephrine reuptake inhibitors (SNRIs) for, 545
Generalized seizures, 487
Genetics, **52–61**
  22q11 deletion syndromes, 61
  autosomal dominant diseases, 56
  autosomal recessive diseases, 56
  autosomal trisomies, 59
  bacterial, **126**, **127**
  chromosome disorders, 60
  code features, **34**
  genetic terms, 52–53
  inheritance modes, 55
  muscular dystrophies, 57
  trinucleotide repeat expansion diseases, 58
  viral, **158–159**
  X-linked recessive disorders, 56
Genetic shift/drift, 165
Genital herpes, 180
Genitalia
  ambiguous, 589, 603, 604
  embryology of, **589**
  estrogen and, 595
  male/female homologs, **590**
Genital tubercles, 590
Genital ulcers, 180
Genital warts, 180
Genitofemoral nerve, 430
Genitourinary drug reactions, **242**
Genotyping microarrays, 50
Gentamicin, 183, 187
  endometritis, 612
Geriatric patients
  amyloidosis in, 213
  atropine in, 233
  Beers criteria in, 238
  changes in, **259**
  colonic ischemia and, 369
  common cause of death, 260
  drug metabolism in, 226
  lipofuscin in, 213
  Medicare for, 260
  nosocomial infections, 181
  osteoporosis, 435
  vascular skin tumors, 450
  volvulus in, 368
  Zenker diverticulum in, 367
Germinal centers of lymph nodes, 92
Germinal center (spleen), 94
Gerstmann syndrome, 481
Gestational age calculation, 598
Gestational diabetes mellitus (GDM), 340
Gestational hypertension, 608
GFAP (glial fibrillary acid proteins), 44
  astrocyte marker, 463
GH. *See* Growth hormone (GH)
Ghon complex
  tuberculosis, 136
Ghon focus, 136
Ghrelin, 317, 356
  hunger and, 466
GHRH. *See* Growth-hormone-releasing hormone
Giant cell arteritis, **302**
Giant cell pneumonia, 166
Giant cells
  in chronic inflammation, 207
Giant cell tumors, 438
Giant cell tumors of bone, 660
Giardia spp
  watery diarrhea, 175
Giardia lamblia, **151**
Giardiasis, 151
Giemsa stain, 122
  Borrelia, 142
  chlamydiae, 146
Gigantism, 317, 333
Gilbert syndrome, 376, 377
Gingival blue line, 652
Gingival hyperplasia
  calcium channel blockers, 304
  cyclosporine, 116
  as drug reaction, 241
  epilepsy drugs and, 514
Gingivostomatitis, 160
Gitelman syndrome, **556**
  markers in, 560
Glans penis, 593
  cancer of, 617
  lymphatic drainage of, 591
Glanzmann thrombasthenia, 393, 405
Glargine insulin, 340. *See also* Insulin
Glaucoma, **506**
  acetazolamide for, 575
  atropine, 233
  β-blockers for, 237
  carbachol for, 232
  diabetes mellitus and, 336
  diagnosing, 232
  drug therapy for, **521**
  epinephrine for, 234
  pilocarpine for, 232
  Sturge-Weber syndrome, 495
Glimepiride, 340
Glioblastoma multiforme, 496
  associations, 664
  labs/findings, 660
  nitrosoureas for, 418
Glioblastomas, 44
Glipizide, 340
Glitazones, 340
Global aphasia, 486
Global payment, 260
Globoid cells
  Krabbe disease, 84, 494
Globose nucleus, 469
Globus pallidus externus, 470
Glomerular diseases
  nomenclature, **563**
Glomerular filtration barrier, **551**
Glomerular filtration rate, **552**, 670
  ACE inhibitor effects, 577
  ANP effect on, 559
  glomerular dynamics in, 553
  juxtaglomerular apparatus, 558
  prerenal azotemia, 571
Glomerulonephritis
  Alport syndrome, 565
  azathioprine for, 116
  bacterial endocarditis, 299
  intrinsic renal failure, 571
  labs/findings, 657, 660, 661
  pharyngitis, 132
  RBC casts in, 562
  Streptococcus pyogenes, 129, 132
  Wegener granulomatosis, 302
Glomerulus
  anatomy of, 550
  dynamics of, **553**
Glomus tumors, 450
Glossitis
  B-complex deficiency, 61
  megaloblastic anemia, 398
  Plummer-Vinson syndrome, 360
  vitamin B$_3$ deficiency, 63
  vitamin B$_9$ deficiency, 64
Glossopharyngeal nerve
  blood flow regulation, 285
Glossopharyngeal nerve (CN IX), **476**
  brain stem location, 474
  branchial arch derivative, 587
  pathway for, 476
  tongue, 463
Glossoptosis, 587
GLP-1 analogs, 341
Glucagon, **315**
  for β-blocker toxicity, 239, 309
  DPP-4 inhibitor effect on, 341

  fructose bisphosphatase-2, 72
  GLP-1 analog effect on, 341
  glucagonomas and, 338
  glycogen regulation, **81**
  insulin and, 314, 315
  production of, 313
  signaling pathways of, 322
  somatostatin and, 356
  somatostatinomas and, 338
Glucagon-like peptide 1 (GLP-1), 314
Glucagonomas, **338**
  MEN 1 syndrome, 339
  somatostatin for, 342
Glucocerebrosidase
  Gaucher disease, 84
Glucocerebroside, 84
Glucocorticoids
  acute gout attack, 661
  adrenal insufficiency, 324
  adrenal steroids and, 318
  arachidonic acid pathway, 455
  calcium pyrophosphate deposition disease, 440
  Cushing syndrome diagnosis, 323
  diabetes mellitus, 336
  fat redistribution with, 241
  gout, 440, 457
  myopathy, 241
  rheumatoid arthritis, 439
  thyroid hormones and, 321
Glucokinase
  hexokinase vs, **71**
  metabolic pathways, 70
Gluconeogenesis, **74**
  cortisol and, 319
  diagram, 70
  ethanol metabolism and, 68
  in insulin deficiency, 336
  metabolic site, 68
  metformin effect on, 340
  pyruvate metabolism and, 73
  rate-determining enzyme for, 69
  thyroid hormones and, 321
Glucose
  ATP production, 71
  blood-brain barrier and, 466
  clearance, **554**
  diabetic ketoacidosis, 337
  GH secretion and, 317
  glycogen metabolism, 82
  insulin and, 314
  metabolism of, 36
  Neisseria fermentation, 138
  for porphyria, 403
  transporters, 314
Glucose-6-phosphatase
  gluconeogenesis, 74
  HMP shunt, 75
  Von Gierke disease, 83
Glucose-dependent insulinotropic peptide (GIP), **356**
Glucosuria
  glucose clearance, 554
  in pregnancy, 554
  SGLT-2 inhibitors, 341
Glulisine insulin, 340. *See also* Insulin
Glutamate
  ammonia transport, 78
  derivatives of, 79
  opioid effects, 520
Glutamic acid, 77
Glutamic acid decarboxylase (GAD-65)
  autoantibodies, 111
Glutathione, 79
  acetaminophen and, 455
  in G6PD deficiency, 400
Glutathione peroxidase, 105
  free radical elimination by, 210
Glutathione reductase, 105
  NADPH and, 71
Gluteus maximus muscle, 431
Gluteus minimus muscle, 431
GLUT transporters, 314
Glyburide, 340
Glyceraldehyde, 76
Glycerol, 76
Glycine
  derivatives of, 79
Glycocalyx, 120
Glycogen, **82**
  insulin and, 314
  periodic acid-Schiff stain, 122
  regulation of, **81**
Glycogenesis
  diagram, 70
  rate-determining enzyme for, 69
Glycogenolysis
  diagram, 70
  in insulin deficiency, 336
  rate-determining enzyme for, 69
  thyroid hormones and, 321
Glycogen phosphorylase
  glycogen metabolism, 82
  glycogenolysis, 69
Glycogen phosphorylase kinase, 81
Glycogen storage diseases, **83**
  Fanconi syndrome, 556
Glycogen synthase, 69
  glycogen metabolism, 82
  glycogen regulation, 81
Glycolysis
  arsenic and, 71
  diagram, 70
  hexokinase/glucokinase in, 71
  metabolic site, 68
  metformin effect on, 340
  pyruvate metabolism and, 73
  rate-determining enzyme for, 69
  regulation of, **72**
  type 2 muscle fibers, 433
Glycopeptides
  mechanism (diagram), 183
Glycoprotein IIb/IIa inhibitors, **415**
Glycoproteins
  bacterial pilus/fimbria, 120
  HIV, 171
  interferons, 200
Glycopyrrolate, 233
Glycosylation, 41
Glycyrrhetinic acid, 556
GNAQ gene, 495
GnRH. *See* Gonadotropin-releasing hormone (GnRH)
Goblet cells, 347, 628
Goiter, **327**
  maternal hypothyroidism from, 328
  maternal iodine deficiency, 582
  in Riedel thyroiditis, 328
Golfer's elbow, 426
Golgi apparatus, 43
  in plasma cells, 389
Gonadal drainage, **591**
Gonadal mosaicism, 53
Gonadotropin, 610
Gonadotropin-releasing hormone
  agonists, 612, 613, 620
  antagonists, 620
  estrogen and, 595
  hypothalamic-pituitary hormones, 315
  Kallmann syndrome, 604
  menopause, 600
  menstrual cycle, 597
  ovulation, 596
  prolactin and, 316
  signaling pathways for, 322
  spermatogenesis, 594
Gonoccal arthritis, 441
Gonococci, vs meningococci, 138
Gonorrhea
  ceftriaxone, 185
  gonococci, 138
  prophylaxis, 194
  STI, 180
Goodpasture syndrome, 46, 564
  autoantibody with, 111
  HLA-DR2, 96
  labs/findings, 657
  restrictive lung disease, 639
  type II hypersensitivity reactions, 108
Good syndrome, 217
Gottron papules, 445
Gout, **440**
  as drug reaction, 241
  drug therapy for, **457**
  kidney stones and, 567
  lab findings, 659, 660
  Lesch-Nyhan syndrome, 34
  loop diuretics and, 575
  presentation, 656
  treatment, 661
  Von Gierke disease, 83
Gower maneuver/sign, 57
Gp41, 199
G-protein-linked 2nd messengers, **230**
Grafts, **114**
Graft-versus-host disease, 115
  type IV hypersensitivity, 109
Gram-negative organisms
  cell wall structure, 120
  cephalosporins, 185
  examples of, 121
  lab algorithm, **137**
Gram-positive cocci antibiotic tests, **130**
Gram-positive organisms
  cell wall structure, 120
  cephalosporins, 185
  examples, 121
  lab algorithm, **130**
  vancomycin, 186
Gram stain identification, **122**
Granular casts, 562
  acute tubular necrosis, 572
Granulocyte-colony stimulating factor (G-CSF), 322
Granulocytes, 386
  morulae, 145
Granulocytopenia
  trimethoprim, 190
Granuloma inguinale, 180
Granulomas, 207
  macrophages and, 387
  TNF-α and, 107
Granulomatosis infantiseptica
  as granulomatous disease, 211
  Listeria monocytogenes, 135
Granulomatous disease, **211**
  Hansen disease, 211
  histoplasmosis, 211
  hypervitaminosis D with, 437
  vitamin D toxicity in, 66
Granulosa cells, 595
  tumors of, 611, 612
Granzyme B
  cytotoxic T cells, 97, 98
  extrinsic pathway and, 204
Grapefruit juice and cytochrome P-450, 243
Graves disease
  autoantibody with, 111
  goiter caused by, 327
  HLA-DR3 and, 96
  hyperthyroidism, 329
  type II hypersensitivity, 108
Gray baby syndrome
  chloramphenicol, 188, 201
  chloramphenicol and, 241
Great cerebral vein of Galen, 473
Greater sac, 346
Greenstick fracture, 424
Grief, 532
Griseofulvin, **196**
  cytochrome P-450 interaction, 243
  microtubules and, 44
  pregnancy contraindication, 201
Ground-glass appearance (X-ray), 173, 627
Growth hormone (GH), **317**, 342
  diabetes mellitus, 336
  ghrelin and, 317
  for hypopituitarism, 335
  insulin resistance and, 314, 317
  Laron syndrome, 333
  secretion of, 313
  signaling pathways for, 322
  somatostatin, 333
  thyroid hormones and, 321
Growth hormone (GH) deficiency, 342

Growth-hormone-releasing hormone
  GH and, 317
  hypothalamo-pituitary hormones, 315
  signaling pathways of, 322
Growth media properties, **122**
Growth signal in cancer, 215
GTPase, 218
GTP (guanosine triphosphate), 73
  smooth muscle contraction, 434
Guaifenesin, 648
Guanfacine, 235
Guanine synthesis, 200
Guanosine analogs
  mechanism and use, **197**
Gubernaculum, 589, 591, 592
Guessing during USMLE Step 1 exam, 21
Guillain-Barré syndrome, 493
  Campylobacter jejuni, 140
  endoneurium in, 465
  presentation, 655
  restrictive lung disease, 639
  Schwann cells in, 464
Gummas
  syphilis, 143, 180
Gustatory hallucinations, 529
Guyon canal syndrome, **426**
Gynecologic tumor epidemiology, **608**
Gynecomastia, **615**
  antiandrogens for, 623
  azoles, 195
  choriocarcinomas, 618
  cimetidine, 381
  cirrhosis, 372
  Klinefelter syndrome, 603
  Leydig cells, 619
  potassium-sparing diuretics, 576
  SHBG and, 322
  spironolactone, 623
  tuberoinfundibular pathway, 468
Gyrase, 183

H

H$_1$ blockers, 242, **648**
H$_2$ blockers, **381**
Haemophilus spp
  endocarditis, 299
  taxonomy, 121
Haemophilus ducreyi
  sexual transmission, 180
Haemophilus influenzae, **138**
  biofilm production, 125
  cephalosporins, 185
  chloramphenicol, 188
  culture requirements, 123
  Gram-negative algorithm, 137
  influenza, 165
  penicillins for, 184
  pneumonia, 175
  postviral infection, 175
  rhinosinusitis, 636
  vaccine, 176
Haemophilus influenzae type B
  chloramphenicol, 188
  encapsulation, 124
  IgA protease, 125
  immunodeficient patients, 114
  meningitis, 176
  rifamycins, 192
  splenic dysfunction, 94
  transformation, 126
  unvaccinated children, 182
  vaccine, 138
Hair
  Menkes disease, 47
  vitamin C deficiency, 65
Hairy cell leukemia, 410
  cladribine for, 417
  IFN-α for, 200
Hairy leukoplakia, 451
  HIV-positive adults, 173
Half-life equation, 225, 669
Halitosis
  Zenker diverticulum, 367
Hallucinations, **529**
  cocaine, 540
  delirium, 528
  memantine, 518
  mesolimbic pathway, 468
  pellagra, 63
  postpartum psychosis, 532
  schizophrenia, 530
  tricyclic antidepressants, 545
Hallucinogen intoxication and withdrawal, 541
Haloperidol, 543
  delirium, 528
  for Huntington disease, 518
  torsades de pointes, 239
Halothane, 519
  hepatic necrosis, 240
Hamartin protein, 218
Hamartomas, 216
  tuberous sclerosis, 495
Hamartomatous colonic polyps, 370
Hamate bone, 426
Hammer toes, 501
Hand
  distortions of, **429**
  gonoccal arthritis triad, 441
  "mechanic's hand," 445
  muscles of, **429**
  squamous cell carcinoma, 454
Hand-foot-mouth disease, 179
Hand grip in auscultation, 278
Hand tremors, 327
Hand-wringing, 527
Hansen disease, **137**
  animal transmission, 144
  dapsone, 190
  erythema nodosum, 453
  as granulomatous disease, 211
Hantavirus, 163
Happy puppet symptoms, 54
Haptens
  acute interstitial nephritis, 572
  amiodarone as, 309
Haptoglobin, 399
Hardy-Weinberg equilibrium, 669
Hardy-Weinberg population genetics, **53**
Hartnup disease, **63**
  vitamin B$_3$ deficiency, 63
Hashimoto thyroiditis, 328
  autoantibody with, 111
  cholangitis association with, 378
  goiter causes, 327
  HLA subtypes with, 96
  lymphoma association, 330
Hassall corpuscles, 94
Hay fever
  HLA-DR2 and, 96
  type I hypersensitivity, 108
HbA$_{1c}$ test, 336
HBcAg (hepatitis B core antigen), 170
HbC disease, 400
  anemia taxonomy, 396
  target cells in, 395
HBeAg (hepatitis B extracellular antigen), 170
HbH disease, 396
HBsAg (hepatitis B surface antigen), 170
hCG. *See* Human chorionic gonadotropin (hCG)
HCTZ. *See* Hydrochlorothiazide (HCTZ)
HDL (high-density lipoprotein), 89
Headaches, **488**
  α-blockers, 236
  bupropion toxicity, 546
  caffeine withdrawal, 540
  Chiari I malformation, 462
  cilostazol/dipyridamole, 415
  cimetidine, 381
  drug adverse effects, 191, 195, 196, 200
  electroconvulsive therapy, 532
  ethosuximide, 514
  genital herpes, 180
  hydralazine, 304
  hypersensitivity pneumonitis, 639
  malaria, 153
  Mucor spp and *Rhizopus* spp, 149
  Mycoplasma pneumoniae, 146
  nitrates, 305
  nonbenzodiazepine hypnotics, 515
  ondansetron, 383
  PDE-5 inhibitors, 623
  pituitary adenomas and, 332
  pituitary apoplexy, 335
  pseudotumor cerebri, 491
  ranolazine, 305
  Rocky Mountain spotted fever, 145
  sodium-channel blockers, 308
  subarachnoid hemorrhage, 656
  triptans for, 516
  vasculitides, 302
Head and neck cancer, **636**
  cetuximab for, 118, 420
Head trauma, 528
Healing, wound, **211**
Healthcare delivery, **259–262**
Healthcare proxy, 257
Health Maintenance Organization, 259
Healthy worker effect, 250
Hearing loss, **503**
  cytomegalovirus, 178
  osteogenesis imperfecta, 47
  Paget disease of bone, 436
Heart
  autonomic nervous system, 229
  autoregulation of, 286
  electrocardiograms, **282**
  embryology, **268**
  fetal development, 580
  ischemia in, 206
  morphogenesis of, **268–269**
  normal pressures in, **286**
  sclerosis of, 446
Heart auscultation, **278**
Heart block, 271
Heartburn, 360
Heart disease
  common cause of death, 260
  congenital, 59, **288–289**
  Fabry disease, 84
  ischemic, 293
  QT prolongation, 72
Heart failure, **298**
  ACE inhibitors for, 577
  acromegaly, 333
  acute tubular necrosis with, 572
  amiodarone, 309
  angiotensin II receptor blockers, 577
  aortic regurgitation as precursor, 279
  associations, 668
  atrial septal defect, 289
  β-blockers, 309
  β-blockers for, 237
  B-type natriuretic peptide in, 285
  calcium channel blockers, 310
  cardiac glycosides for, 307
  chronic ischemic heart disease, 293
  contractility in, 273
  diabetic ketoacidosis, 337
  disopyramide, 308
  dobutamine for, 234
  dopamine for, 234
  Ebstein anomaly, 288
  ejection fraction in, 273
  ESR in, 212
  fludrocortisone and, 342
  glitazone/thiazolidinediones, 340
  hydralazine for, 304
  hypertension, 290
  hypertension treatment in, 304
  hypertensive emergency and, 290
  jugular venous pulse in, 276
  loop diuretics for, 575
  MI, 294
  pleural effusion, 644
  potassium-sparing diuretics, 576
  pulse pressure in, 272
  readmissions with, 261
  renal failure causing, 571
  shock caused by, 299
  sleep apnea causing, 642
  systolic vs diastolic, 273
  thiazides for, 576
  ventricular septal defect, 289
Heart murmurs, **279**
  aortic regurgitation, 652
  aortic stenosis, 656
  auscultation of, 278

  bacterial endocarditis, 299
  cardiomyopathies, 297
  patent ductus arteriosus, 289
Heart rate, 235
Heart sounds, **276**
  associations, 668
  auscultation of, 278
  cardiac cycle, 276
  cardiac tamponade, 300, 654
  splitting in, **277**
Heart transplant
  dilated cardiomyopathy, 297
Heart valve development, 269
Heat-labile toxin, 128
Heat shock proteins, 41
Heat-stable toxin, 128
Heinz bodies, 75, 395, 400
Helicase, **35**
Helicobacter spp, 121
Helicobacter pylori, **142**
  associations, 664
  catalase-positive organism, 124
  disease associated with, 362
  Gram-negative algorithm, 137
  metronidazole, 191
  as oncogenic microbe, 219
  penicillins for, 184
  silver stain, 122
  urease-positive, 124
  urease-positive organism, 124
Heliotrope rash, 445
HELLP syndrome, 608
  schistocytes in, 395
Helminthic infections
  eosinophils and, 387
Helminths
  immune response to, 154
Helper T cells, **98**
  cell surface proteins, 106
  cytokine secretion, 104
  in granulomatous diseases, 211
Hemagglutinin
  influenza viruses, 165
  parainfluenza viruses, 166
Hemangioblastomas, 496
  polycythemia and, 217
  von Hippel-Lindau disease, 495, 655
Hemangiomas, 216
Hemarthroses, 404
Hemarthrosis, 65
Hematemesis, 360
  Mallory-Weiss syndrome, 656
Hematin, 123, 138
Hematochezia
  colorectal cancer, 371
  diverticulosis, 366
  intestinal disorders, 369
  Meckel diverticulum, 585
Hematocrit
  high altitude and, 635
  polycythemia vera, 411
Hematologic drug reactions, 241
Hematology/oncology, **386–423**
  anatomy, 386–389
  pathology, 394–414
  pharmacology, 413–421
  physiology, 389–393
Hematopoiesis, 409
Hematopoietic stem cells, 106
Hematuria
  bladder cancer, 569
  Henoch-Schönlein purpura, 655
  hereditary hemorrhagic telangiectasia, 303
  IgA nephropathy, 564
  kidney stones, 567
  nephritic syndrome, 564
  Osler-Weber-Rendu syndrome, 656
  protease inhibitors, 199
  renal cell carcinoma, 568
  renal cyst disorders, 573
  renal oncocytomas, 568
  RPGN, 564
  Schistosoma haematobium, 157
  UTIs, 177
  Wegener granulomatosis, 302
  Wilms tumor, 569
Heme
  bilirubin and, 359
  chloroquine, 196
  for porphyria, 403
  sideroblastic anemia and, 397
  synthesis of, 68, **403**
  vitamin B_6 and, 63
Hemianopia, 511
Hemiballismus, 489
  brain lesions and, 481
Hemicholinium, 231
Hemidesmosome, 447
  autoantibody to, 111
Hemihyperplasia, 569
Hemiparesis, 493
  saccular aneurysms, 486
Hemispatial neglect syndrome, 481
Hemochromatosis, **378**
  calcium pyrophosphate deposition disease, 440
  cardiomyopathy from, 297
  chromosome association, 60
  free radical injury and, 210
  hepatocellular carcinoma and, 375
  HLA-A3 and, 96
Hemoglobin, **631**
  carbon dioxide transport, 635
  development of, 389
  kinetics of, 224
  modifications of, **632**
Hemoglobin electrophoresis, **391**
Hemoglobinuria
  acute tubular necrosis and, 572
  G6PD deficiency, 400
  intravascular hemolysis, 399
Hemolysis
  alpha toxin as cause, 129
  Clostridium perfringens as cause, 134
  HELLP syndrome, 608
  sulfonamides as cause, 190
Hemolysis in G6PD deficiency, 241
Hemolytic anemia, 399
  autoimmune, 108, 185
  babesiosis, 153
  cephalosporins, 185
  cold agglutinin disease, 655
  direct Coombs-positive, 241
  folate deficiency caused by, 398
  G6PD deficiency, 75
  in taxonomy, 396
  penicillin G, V, 183
  pyruvate kinase deficiency as cause, 400
  ribavirin, 200
  spherocytes in, 395
  sulfa drug allergies, 243
  vitamin E deficiency, 66
  Wilson disease, 378
Hemolytic disease of the newborn, 108
Hemolytic reactions and blood types, 390
Hemolytic-uremic syndrome
  Escherichia coli, 140, 175
  exotoxins, 128
  platelet disorders, 405
  schistocytes in, 395
Hemophilia, 404
  deficiencies causing, 391
  X-linked recessive disorder, 56
Hemoptysis
  Aspergillus fumigatus, 173
  bronchiectases, 639
  choriocarcinomas, 605
  lung cancer, 647
  tuberculosis, 136
  Wegener granulomatosis, 302
Hemorrhage
  acute pancreatitis, 380
  acute tubular necrosis, 572
  AIDS retinitis, 161
  baroreceptors and, 285
  bevacizumab, 420
  delirium caused by, 528
  Ebola virus, 167
  intracranial, **483**
  pulmonary, 133
  shock from, 299
  subarachnoid hemorrhage, 483, 486
  ulcers, 363
  Weil disease, 142
Hemorrhagic cystitis
  adenoviridae, 160
  cyclophosphamide, 418
  drug reaction, 242
Hemorrhagic fever
  bunyavirus, 163
  filovirus, 163
Hemorrhagic infarcts, 207
Hemorrhagic stroke, 483
Hemorrhoids, 351
Hemosiderinuria, 399
Hemostasis, 386
Henderson-Hasselbalch equation, 561, 670
Henoch-Schönlein purpura, **303**
  IgA nephropathy, 564
  presentation, 655
Hepadnaviruses
  characteristics of, 159, 160
  genome, 158
Heparin, **413**
  acute coronary syndromes, 296
  for anticoagulation, 391
  in basophils, 387
  in coagulation cascade, 392
  deep venous thrombosis, 636
  mast cells and, 387
  osteoporosis, 241
  thrombocytopenia, 241
  toxicity treatment, 239
  warfarin vs, **414**
Heparin-induced thrombocytopenia (HIT), 413
Hepatic adenomas, 375
Hepatic arteries, 349, 352
Hepatic ascites, 576
Hepatic cirrhosis, 644
Hepatic ducts, 353
Hepatic encephalopathy, **374**
  cirrhosis, 372
Hepatic necrosis, 455
Hepatic steatosis, 374
Hepatic TG lipase, 88
Hepatitis
  alcoholic, 374
  alcoholism, 541
  aplastic anemia and, 399
  autoimmune, 111
  cirrhosis, 372
  as drug reaction, 240
  heroin addiction and, 541
  hyperbilirubinemia, 376
  Wilson disease, 378
Hepatitis A (HAV)
  characteristics of, **168**
  picornavirus, 163, 164
  serologic markers, 170
  vaccine for, 107, 158
Hepatitis antigens, **170**
Hepatitis B (HBV)
  characteristics of, **168**
  extrahepatic manifestations, 169
  hepatocellular carcinomas and, 375
  IFN-α, 200
  medical importance, 160
  membranous nephropathy, 566
  MPGN and, 565
  nosocomial infection, 181
  as oncogenic microbe, 219
  passive antibodies for, 107
  polyarteritis nodosa and, 302
  recombinant cytokines for, 117
  serologic markers, 170
  sexually transmitted infection, 180
  treatment, 661
Hepatitis C (HCV)
  antigenic variation, 106
  characteristics of, **168**
  extrahepatic manifestations, 169
  flaviviruses, 163
  hepatocellular carcinoma and, 375
  lichen planus, 453
  membranous nephropathy, 566
  MPGN and, 565
  as oncogenic microbe, 219
  recombinant cytokines for, 117
  therapy for, **200**

- Hepatitis D (HDV), **168**
- Hepatitis E (HEV), **168**
  - hepevirus, 163
- Hepatitis viruses, **168**
  - aplastic anemia, 399
  - serologic markers for, 170
- Hepatocellular carcinomas, **375**
  - *Aspergillus fumigatus*, 149
  - Budd-Chiari syndrome and, 375
  - carcinogens causing, 219
  - cirrhosis and, 372
  - hemochromatosis, 378
  - non-alcoholic fatty liver disease, 374
  - oncogenic microbes, 219
  - polycythemia and, 217
- Hepatocytes, 82
- Hepatoduodenal ligament, 346
- Hepatomas, **375**
- Hepatomegaly
  - amyloidosis and, 213
  - Budd-Chiari syndrome, 375, 652
  - galactosemia, 76
  - hepatocellular carcinoma, 375
  - peroxisomal disease, 43
  - pulmonary hypertension, 633
  - Reye syndrome, 373
  - right heart failure, 298
  - Von Gierke disease, 83
- Hepatosplenomegaly
  - β-thalassemia and, 397
  - biliary tract disease, 378
  - graft-versus-host disease, 115
  - hyperchylomicronemia, 90
  - leishmaniasis, 154
  - lysosomal storage diseases, 84
  - mononucleosis, 161
  - ToRCHeS infections, 178
- Hepatotoxicity
  - amiodarone, 309
  - bosentan, 648
  - carbamazepine, 514
  - danazol, 622
  - glitazone/thiazolidinediones, 340
  - HMG-CoA reductase inhibitors, 306
  - inhaled anesthetics, 519
  - isoniazid, 193
  - leflunomide, 456
  - methotrexate, 417
  - pyrazinamide, 193
  - rifamycins, 192
  - terbinafine, 195
  - thionamides, 341
  - valproic acid, 514
  - zileuton, 649
- Hepcidin
  - acute-phase reactant, 102
  - in anemia of chronic disease, 399
- Hepeviruses
  - characteristics, 163
  - genomes, 159
  - naked viruses, 159
- HER-2, 616
- "Herald patch" in pityriasis rosea, 453
- Herceptin(trastuzumab), 421
- Hereditary angioedema, 622
- Hereditary hemorrhagic telangiectasia, 303
- Hereditary hyperbilirubinemias, **377**
- Hereditary spherocytosis, 400
  - in anemia taxonomy, 396
  - spherocytes in, 395
- Hereditary thrombosis syndromes, **406**
- Heritable amyloidosis, 213
- Hermaphrodites, 604
- Hernias, **355**
  - site of, 354
- Herniation syndromes, **499**
- Heroin
  - addiction to, **541**
  - focal segmental glomerulosclerosis, 566
  - intoxication and withdrawal, 540
  - opioids for withdrawal, 520
- Herpes encephalitis, 48
- Herpes genitalis, 160
- Herpes labialis, 160
- Herpes simplex virus 1 (HSV-1), 160, 451
  - encephalitis, 668
  - STI, 180
- Herpes simplex virus 2 (HSV-2), 160, 451
  - STI, 180
  - ToRCHeS infection, 178
- Herpes simplex virus (HSV)
  - cidofovir, 198
  - erythema multiforme, 452
  - foscarnet for, 198
  - guanosine analogs, 197
  - identification, 162
  - meningitis caused by, 176
  - retinitis, 508
- Herpesviruses, **160–162**, 451
  - clinical significance, 160
  - envelope, 159
- Herpes zoster
  - dorsal root latency, 160
  - famciclovir, 197
  - retinitis, 508
- Herpetic whitlow, 160
- Hesselbach triangle, 355
- Heterochromatin, **32**
- Heterodimer, 44
- Heterodisomy, 53
- Heterogeneous nuclear RNA (hnRNA), 38
- Heteroplasmy, **53**
- Heterozygosity loss, 52
- Hexokinase
  - glucokinase vs, **71**
  - metabolic pathways, 70
- *HFE* gene
  - hemochromatosis and, 378
- HGPRT, 417
- HGPRT (hypoxanthine guanine phosphoribosyltransferase), 34
- HHNS, 338
- Hiatal hernias, 355
- Hiccups, 489
- High altitude respiratory response, 635
- High-frequency recombination (Hfr) cells, 126
- Highly active antiretroviral therapy (HAART), 199
- Hilar adenopathy, 652
- Hilar lymphadenopathy, 639
- Hilar lymph nodes, 93
  - silicosis, 641
- Hilar nodes, 136
- Hindbrain, 460
- Hindgut
  - blood supply/innervation of, 348
  - development of, 344
- Hip dislocation
  - nerve injury with, 431
- Hip muscles, 431
- Hippocampus
  - lesions in, 481
  - limbic system, 468
  - pyramidal cells, 206
- Hippurate test, for *Streptococcus agalactiae*, 133
- Hirschsprung disease, **367**
  - Down syndome, 59
- Hirsutism
  - cyclosporine, 116
  - danazol, 622
  - epilepsy drugs and, 514
  - menopause, 600
  - PCOS, 609
  - SHBG and, 322
- Hirudin, 413
- Histaminase, 387
- Histamine receptors, 230
- Histamines
  - in basophils, 387
  - cortisol effect on, 319
  - derivatives of, 79
  - location of, 357
  - mast cells and, 387
  - seafoor toxins, 238
  - signaling pathways for, 322
  - vitamin B_6 and, 63
- Histidine, 77
  - derivatives of, 79
- Histocompatibility complex I and II, **107**
- Histone acetylation, **32**
- Histone methylation, **32**
- Histones
  - autoantibody, 111
- *Histoplasma* spp
  - treatment, 195
- *Histoplasma capsulatum*
  - HIV-positive adults, 173
  - necrosis and, 205
- Histoplasmosis, **147**
  - as granulomatous disease, 211
  - erythema nodosum, 453
  - as granulomatous disease, 211
- Histrionic personality disorder, 535
- HIV (human immunodeficiency virus), **171**
  - antigenic variation, 106
  - aplastic anemia in, 399
  - cervical cancer and, 609
  - diagnosis, **171**
  - disease associations, 173
  - ex vacuo ventriculomegaly, 492
  - flow cytometry diagnosis, 50
  - focal segmental glomerulosclerosis, 566
  - hairy leukoplakia, 451
  - heroin addiction and, 541
  - Kaposi sarcoma, 161, 450
  - lymphopenia, 402
  - meningitis, 176
  - microglia in, 463
  - non-Hodgkin lymphoma and, 407
  - PCR diagnosis, 48
  - *Pneumocystis jirovecii*, 150
  - primary central nervous system lymphoma (PCL) and, 408
  - prophylaxis for HIV patients, **194**
  - pulmonary arterial hypertension, 643
  - retrovirus, 163
  - rifamycins in, 192
  - STI, 180
  - T cells and, 388
  - therapy for, 197, **199**
  - ToRCHeS infection, 178
  - untreated time course, 172
  - vaccination, 107
  - viral receptor, 162
  - Western blot diagnosis, 49
- HIZ shrinkage in muscle contraction, 433
- HLA genes, **96**
  - associations, 656, 657
  - celiac disease and, 364
  - disease associations, 328
  - DM type 1 association, 337
  - seronegative spondyloarthritis, 442
  - uveitis, 506
- HMG-CoA reductase
  - cholesterol synthesis, 69
  - metabolic pathways, 70
- HMG-CoA reductase inhibitors, 306
  - naming conventions, 244
- HMG-CoA synthase, 69
- HMP shunt, **75**
  - diagram, 70
  - metabolic site, 68
  - NADPH production, 71, 75
  - rate-determining enzyme, 69
  - Vitamin B_1 deficiency, 62
- Hoarseness
  - gastroesophageal reflux disease as cause, 360
  - heart enlargement, 271
  - lung cancer, 647
  - Pancoast tumor, 646
- "Hobnail" liver in alcoholic cirrhosis, 374
- Hodgkin lymphoma
  - bleomycin for, 418
  - non-Hodgkin vs, **407**
  - oncogenic microbes and, 219
  - paraneoplastic cerebellar degeneration and, 217

  types of, 668
  vinca alkaloids for, 419
Holoprosencephaly, 461
  fetal alcohol syndrome, 583
  Patau syndrome, 59
  Sonic hedgehog gene and, 580
Homan sign, 636
Homatropine, 233
Homeobox genes, 580
Homer-Wright rosettes, 498
Homicide, as common cause of death, 260
Homocysteine
  B_{12} deficiency, 398
  folate deficiency, 398
  vitamin B_9 deficiency, 64
  vitamin B_{12} deficiency, 65
Homocysteine methyltransferase
  deficiency in, 80
  vitamin B_{12} and, 65
Homocystinuria, **80**
Homovanillic acid (HVA)
  in neuroblastomas, 325
  tyrosine catabolism, 79
Homunculus, **471**
Hookworms, 155
Hormone replacement therapy, **621**
  endometrial hyperplasia, 612
  estrogens for, 621
  for hypopituitarism, 335
  thrombotic complications, 241
Hormone-sensitive lipase, 88
Hormones (reproductive), **620**
Horn cysts, 449
Horner syndrome, 488, **509**
  labs/findings, 657
  lung cancer, 647
  Pancoast tumor, 646
  presentation, 655
Horner-Wright rosettes, 325
Horse flies (disease vector), 155
Horseshoe kidney, **549**
  Turner syndrome, 656
Hospice care, 260
Hospital readmissions, causes of, **261**
Hot flashes
  as drug reaction, 240
  menopause, 600
"Hourglass stomach," 355
Howell-Jolly bodies, 395, 657
  postsplenectomy, 94
Hu antigens, 217
Human chorionic gonadotropin (hCG), **598**
  choriocarcinomas, 605, 618
  ectopic pregnancy, 607
  embryonal carcinomas, 618
  hydatidiform moles, 605
  pregnancy, 598
  secretion of, 580
  signaling pathways, 322
Human factors design, **261**
Human growth hormone. *See* Growth hormone (GH)
Human herpesvirus 6 (HHV-6), 161, 179
Human herpesvirus 7 (HHV-7), 161
Human herpesvirus 8 (HHV-8), 161, 173
  Kaposi sarcoma, 450
  as oncogenic microbe, 219
Humanized monoclonal A_b, 244
Humanized monoclonal antibodies, 107
Human papillomavirus 6 (HPV-6), 180
Human papillomavirus 11 (HPV-11), 180
Human papillomavirus 16 (HPV-16), 636
Human papillomavirus (HPV)
  cervical pathology, 609
  HIV-positive adults, 173
  as oncogenic microbe, 219
  penile cancer, 617
  tumor epidemiology, 608
  verrucae, 449
  warts, 160
Human placental lactogen, 598
Humerus injury
  axillary nerve and, 427
  median nerve injury, 427
  radial nerve and, 427
Humor, 525
Hunger, 466
Hunter syndrome, 56, 84
Huntington disease, 529
  basal ganglia lesions, 481
  neurodegenerative disorder, 490
  neurotransmitters for, 465
  treatment, **518**
  ventromegaly, 492
Hurler syndrome, 84
Hürthle cells, 328
Hutchinson teeth, 143
Hyaline arteriolosclerosis, 291
Hyaline casts, 562
Hyaline membrane disease, 639
Hydatid cysts, 157
Hydatidiform moles, **605**
  hCG in, 598
  theca-lutein cysts and, 610
Hydralazine, **304**
  gestational hypertension, 304, 608
  heart failure, 298
  lupus-like syndrome, 241
Hydrocephalus, **492**
  childhood tumors, 498
  dementia, 529
  headaches with, 488
  posterior fossa malformations, 462
  risk for developing, 483
  Toxoplasma gondii, 178
  toxoplasmosis, 152
  vertical gaze paralysis, 481
Hydrochlorothiazide (HCTZ), 576
  for diabetes insipidus, 334
  hyperglycemia, 240
  pancreatitis, 240
Hydrocortisone
  arachidonic acid pathway, 455
Hydrogen peroxide, 200
Hydronephrosis, **568**
  BPH, 619
  horseshoe kidney, 549
  kidney stones, 567
Hydrophobia, 167
Hydrops fetalis
  α-thalassemia as cause, 396
  parvovirus, 160
  parvovirus B19, 178, 179
  syphilis, 178
Hydrosalpinx, 181
Hydrothorax, 610
Hydroxychloroquine
  lupus, 443
  myopathy, 241
  rheumatoid arthritis, 439
Hydroxylases, 69
Hydroxylation, 41
Hydroxyurea, **419**
  in cell cycle, 416
  polycythemia vera, 411
  pruine synthesis, 33
  sickle cell anemia, 400
  targets of, 416
Hyoid artery, 586
Hyoscyamine, 233
Hyperactivity, 327
Hyperacute transplant rejection, 115
Hyperaldosteronism, **324**
  hypertension with, 290
  metabolic alkalosis, 561
  potassium-sparing diuretics for, 576
Hyperammonemia, **78**
Hyperbilirubinemia
  cirrhosis as cause, 372
  hereditary, **377**
  jaundice and, 376
Hypercalcemia, 560
  acute pancreatitis caused by, 380
  adult T-cell lymphoma, 408
  bisphosphonates for, 456
  calcium carbonate as cause, 382
  diabetes insipidus, 334
  granulomatous diseases and, 211
  hyperparathyroidism, 332
  loop diuretics for, 575
  lung cancer, 647
  paraneoplastic syndrome, 217
  PTH-independent, 331
  sarcoidosis and, 444
  succinylcholine, 520
  teriparatide, 457
  thiazides as cause, 576
  vitamin D toxicity, 66
  Williams syndrome, 60
Hypercalciuria
  hyperparathyroidism, 332
  thiazides for, 576
  vitamin D toxicity, 66
Hypercapnia
  contractility in, 273
Hypercholesterolemia, 90
  hypothyroidism, 327
  nephrotic syndrome, 655
  presentation, 652
Hyperchylomicronemia, 90
Hypercoagulability
  hereditary syndromes, **406**
  pregnancy, 598
  warfarin adverse effect, 414
Hyperemesis gravidarum, 605
Hyperemia
  pseudoepherine/phenylephrine, 648
Hyperestrogenism, 610
Hyperglycemia. *See also* Diabetes mellitus
  Cushing syndrome, 323
  diabetic ketoacidosis, 337
  diabetic retinopathy, 507
  as drug reaction, 240
  glucagon and, 315
  hyperkalemia, 560
  immunosuppressants, 116
  niacin causing, 306
  pancreatic cell tumors, 338
  protease inhibitors, 199
  thiazides, 576
  vitamin B_3 toxicity, 63
Hypergranulosis, 448
Hyper-IgE syndrome
  presentation, 655
Hyper-IgM syndrome, 113
Hyperinsulinemia, 609
Hyperkalemia, 560
  aliskiren, 577
  angiotensin II receptor blockers, 577
  cardiac glycosides, 307
  causes of, 560
  diabetic ketoacidosis, 337
  potassium-sparing diuretics, 576
  primary adrenal insufficiency, 324
  renal failure, 571
  SGLT2 inhibitors, 341
Hyperkalemic renal tubular acidosis, 562
Hyperkeratosis, 448, 449
Hyperlipidemia, **291**
  atherosclerosis and, 292
  atypical antipsychotics, 543
  glomerular filtration barrier and, 551
  immunosuppressants, 116
  nephrotic syndrome, 566
  thiazides, 576
Hypermagnesemia, 560
Hypernatremia, 560
Hyperopia, 504
Hyperorality
  Klüver-Bucy syndrome, 481
Hyperosmolar coma
  DM type 2, 336
Hyperosmolar hyperglycemic state, **338**
Hyperosmolarity, 560
Hyperparathyroidism, **332**
  associations, 668
  calcium pyrophosphate deposition disease, 440
  cinacalcet for, 342
  lab findings, 657
  lab values in, 437

Hyperparathyroidism *(continued)*
  osteoporosis, 435
  renal osteodystrophy and, 571
Hyperphagia
  depression with, 531
  hypothalamus and, 466
  Klüver-Bucy syndrome, 481
  Prader-Willi syndrome, 54
Hyperphosphatemia, 560
  hyperparathyroidism (secondary), 332
  hypoparathyroidism, 331
  renal osteodystrophy and, 571
Hyperpigmentation
  adrenocortical insufficiency, 656
  bleomycin, 418
  busulfan, 418
  fludrocortisone, 342
  hemochromatosis as cause, 378
  melasma, 448
  Peutz-Jeghers syndrome as cause, 370
  primary adrenal insufficiency, 324
Hyperplasia, 214, 215
  adrenal, 323, 324
  parathyroid, 331, 332, 339
Hyperplastic arteriolosclerosis, 291
Hyperplastic polyps, 370
Hyperprolactinemia, 315, 496
  anovulation, 609
  calcium channel blockers as cause, 304
  risperidone as cause, 543
Hyperpyrexia
  tricyclic antidepressants, 545
Hyperreflexia
  serotonin syndrome, 545
Hyperresonance, 644
Hypersensitivity pneumonitis, 211, 639
Hypersensitivity reactions, **108–109**
  blood transfusions, 110
  C3 deficiency, 103
  cephalosporins, 185
  Graves disease, 329
  helminths, 154
  IgE antibodies, 101
  to insulin, 340
  mast cells and, 387
  organ transplants, 115
  penicillins, 183, 184
  rheumatic fever, 300
  sulfonamides, 190
Hypersexuality
  Klüver-Bucy syndrome, 481
Hypersomnia, 531
Hypertension, **290**
  ACE inhibitors for, 577
  acute poststreptococcal glomerulonephritis, 564
  alcohol withdrawal, 541
  aliskiren for, 577
  α-blockers for, 236
  angiotensin II receptor blockers for, 577
  aortic dissection and, 293, 664
  atherosclerosis and, 292
  atrial fibrillation and, 284
  autosomal recessive polycystic kidney disease, 573
  β-blockers for, 237
  calcium channel blockers for, 304
  Charcot-Bouchard microaneurysms, 486
  Cushing syndrome, 323
  diabetes mellitus, 304
  endometrial cancer, 612
  Guillain-Barré syndrome, 493
  heart failure, 304
  hydralazine for, 304
  hyperaldosteronism, 324
  immunosuppressants, 116
  intraparenchymal hemorrhage, 483
  leflunomide, 456
  local anesthetics, 519
  loop diuretics for, 575
  MDMA, 541
  microangiopathic anemia, 401
  minoxidil, 623
  nephritic syndrome and, 564
  PCP, 541
  pheochromocytomas, 326
  placental abruption, 606
  polyarteritis nodosa, 302
  preeclampsia, 608
  in pregnancy, 235, 304
  pregnancy, **608**
  pseudoepherine/phenylephrine, 648
  renal cyst disorders, 573
  renal failure, 571
  sleep apnea, 642
  syndrome of apparent mineralocorticoid excess, 556
  thiazides for, 576
  thoracic aortic aneurysms and, 292
  treatment for, **304**
  tyramine, 236
  tyramine ingestion, 546
Hypertensive crisis
  MAO inhibitors as cause, 546
  phenoxybenzamine for, 236
Hypertensive emergency, 290, **304**
Hypertensive nephropathy, 290
Hypertensive urgency, 290, 304
Hyperthermia
  atropine as cause, 233
  MDMA, 541
  serotonin syndrome, 545
Hyperthyroidism, **329**, 610
  amiodarone and, 309
  choriocarcinomas, 618
  hCG, 598
  hydatidiform moles, 605
  hypothyroidism vs, **327**
  mature cystic teratoma, 610
  osteoporosis, 435
  pulse pressure in, 272
  thionamides for, 341
Hypertonia
  serotonin syndrome, 545
Hypertriglyceridemia, 90
  acute pancreatitis caused by, 380
Hypertrophic cardiomyopathy, 297
  Pompe disease, 83
  systolic murmur in, 278
Hypertrophic osteoarthropathy, 647
Hypertrophic pyloric stenosis, **345**
Hypertrophic scars, 210
Hypertrophy, 214
Hypertropic cardiomyopathy, 501
Hyperuricemia
  as drug reaction, 241
  gout, 440
  kidney stones and, 567
  Lesch-Nyhan syndrome, 34
  niacin and, 306
  pyrazinamide, 193
  thiazides, 576
  vitamin B_3 toxicity, 63
Hyperventilation
  emphysema, 655
  metabolic acidosis, 561
  pregnancy, 598
Hypervitaminosis D, 437
Hypnagogic hallucinations, 529
  narcolepsy, 538
Hypnopompic hallucinations, 529
  narcolepsy, 538
Hypoalbuminemia
  alcoholic cirrhosis as cause, 374
  nephrotic syndrome, 563, 566, 655
Hypocalcemia, 319, 560
  22q11 deletion syndromes, 61
  acute pancreatitis as cause, 380
  cinacalcet causing, 342
  DiGeorge syndrome, 588
  hypermagnesemia and, 560
  hyperparathyroidism, 332
  hypoparathyroidism, 331
  pseudohypoparathyroidism, 331
  renal osteodystrophy, 571
  thymic aplasia, 112
  thyroidectomy, 330
Hypocalcemic tetany, 66
Hypocholesterolemia
  hyperthyroidism, 327
Hypocitraturia, 567
Hypocretin, 538
Hypodermis, 446
Hypofibrinogenemia, 212
Hypogammaglobulinemia, 217
Hypoglossal canal, 476
Hypoglossal nerve (CN XII), **476**
  brain stem location, 474
  lesion in, 502
  location in brain stem, 474
  pathway, 476
  tongue, 463
Hypoglycemia
  amylin analogs, 341
  carnitine deficiency, 85
  fructose intolerance, 76
  GH secretion in, 317
  glucagon production with, 315
  gluconeogenesis and, 74
  insulin as cause, 340
  insulinomas, 338
  loss of orientation, 528
  low birth weight and, 599
  meglitinides, 341
  neonatal, 582
  Reye syndrome as cause, 373
  somatostatinomas, 338
  sulfonylureas, 340
  Von Gierke disease, 83
Hypoglycemic drugs, **340–341**
Hypogonadism
  diagnosis of, 604
  estrogens for, 621
  gynecomastia, 615
  hemochromatosis as cause, 378
  Kallmann syndrome, 604
  Klinefelter syndrome, 603
  pituitary prolactinomas, 315
  Prader-Willi syndrome, 54
  testosterone/methyltestosterone, 623
  zinc deficiency, 67
Hypogonadotropic hypogonadism, 604
Hypokalemia, 560
  antacids as cause, 382
  Bartter syndrome, 556
  causes of, 560
  cystic fibrosis, 56
  on ECG, 282
  Gitelman syndrome, 556
  loop diuretics, 575
  nephrogenic DI, 334
  syndrome of apparent mineralocorticoid excess as cause, 556
  VIPomas as cause, 356
Hypomagnesemia, 560
Hypomania, 531
Hypomanic episodes, **531**
Hyponatremia, 560
  cirrhosis as cause, 372
  MDMA as cause, 541
  osmotic demyelination syndrome, 492
  as paraneoplastic syndrome, 217
  thiazides, 576
Hypoparathyroidism, **331**
Hypophosphatemia, 560
  aluminum hydroxide as cause, 382
  hyperparathyroidism, 332
Hypophosphatemic rickets, 55
Hypopituitarism, **335**
  pituitary adenomas, 332
Hypoproteinemia, 551
Hyporeflexia
  LMN lesions, 501
  magnesium hydroxide as cause, 382
Hypospadias, 591
Hyposplenia, 395
Hypotension
  acute tubular necrosis with, 572
  adrenal insufficiency, 324
  adrenocortical insufficiency, 656
  aliskiren, 577
  amphotericin B, 195
  angiotensin II receptor blockers, 577

  cardiac tamponade, 300
  cilostazol/dipyridamole, 415
  endotoxins, 127
  ephedrine for, 234
  Guillain-Barré syndrome, 493
  hypermagnesemia, 560
  local anesthetics, 519
  magnesium hydroxide as cause, 382
  metronidazole, 191
  midodrine for, 234
  norepinephrine for, 234
  orthostatic, 324
  phenylephrine for, 234
  scombroid poisoning, 238
  SGLT2 and, 341
  sympatholytic drugs and, 235
  Waterhouse-Friderichsen syndrome, 652
Hypothalamic/pituitary drugs, **342**
Hypothalamic-pituitary hormones, **315**
Hypothalamus, **466**
  ADH secretion, 317
  sleep physiology, **467**
  TRH and, 321
Hypothenar muscles, 429
  Klumpke palsy, 428
Hypotheses (statistical), 251
  testing, 252
Hypothyroidism, **328**
  amiodarone and, 309
  anemia, 398
  in anemia taxonomy, 396
  carpal tunnel syndrome and, 426
  dementia, 529
  as drug reaction, 240
  hormone replacement, 342
  hyperthyroidism vs, **327**
  lithium, 544
Hypotonia
  carnitine deficiency, 85
  Menkes disease, 47
  Prader-Willi syndrome, 54
Hypoventilation, 561
Hypovolemia, 336
Hypovolemic shock, 299
Hypoxanthine, 457
Hypoxanthine guanine phosphoribosyltransferase (HGPRT), 34
Hypoxemia
  alveolar gas equation, 634
  obstructive lung disease, 638
  oxygen deprivation, **634**
  pulmonary emboli, 637
  respiratory alkalosis and, 561
Hypoxia
  apoptosis caused by, 204
  contractility in, 273
  erythropoietin and, 559
  hemoglobin modifications, 632
  lung diseases, 643
  nocturnal, 642
  oxygen deprivation, 634
  regions susceptible to, 206
  renal, 632
  vasoconstriction/vasodilation and, 286
Hypoxia inducible factor 1a, 218
Hypoxic stroke, 482
Hysterectomy
  adenomyosis, 612
  cardinal ligament in, 592
Hysteresis (lung and chest wall), 631
Hysteria
  respiratory alkalosis from, 561

I

Iatanoprost, 521
Ibandronate, 456
Ibuprofen, 456
  arachidonic acid pathway and, 455
  hemolysis in G6PD deficiency, 241
Ibutilide, 309
ICAM-1 protein
  in leukocyte extravasation, 209
  viral receptor, 162
I-cell disease, **43**
I cells, 356
Icosahedral viruses, 159
Idealization, 525
Identification, 525
Idiopathic intracranial hypertension, **491**
Idiopathic thrombocytopenic purpura (ITP)
  labs/findings, 657
  rituximab for, 118, 420
  type II hypersensitivity reactions, 108
IDL (intermediate-density lipoprotein), 89
IFN-α (Interferon-α), **105**
  clinical uses, 117
  natural killer cells, 97
IFN-α (interferon-α)
  clinical use, 200
  hepatitis, 661
IFN-β (Interferon-β), **105**
  clinical uses, 117, 200
  natural killer cells, 97
IFN-γ (Interferon-γ), 104, 112
  cachexia and, 221
  clinical uses, 117, 200
  granulomatous diseases and, 211
  Graves disease and, 329
  helper T cells, 98
Ifosfamide, 418
  Fanconi syndrome, 556
  hemorrhagic cystitis, 242
IgA antibodies, 101
  ataxia-telangiectasia, 113
  breast milk, 599
  in celiac disease, 364
  deficiency in, 112, 652
  hyper-IgM syndrome, 113
  multiple myeloma production of, 409
  passive immunity, 107
  Peyer patches and, 358
IgA nephropathy, 564
  Henoch-Schönlein purpura and, 303
IgA protease, 125
IgD antibodies, 101
IgE antibodies, 101
  ataxia-telangiectasia, 113
  eczema, 449
  hyper-IgM syndrome, 113
  mast cells and, 387
  type I hypersensitivity, 108
IGF-1. *See* Insulin-like growth factor 1 (IGF-1)
IgG antibodies, 101
  anemia and, 401
  ataxia-telangiectasia, 113
  bullous pemphigoid, 452
  complement activation and, 103
  hepatitis A (HAV), 170
  hyper-IgM syndrome, 113
  multiple myeloma production of, 409
  multiple sclerosis, 493
  as passive immunity, 107
  pemphigus vulgaris, 452
  in pregnancy, 390
  in type III hypersensitivity reactions, 109
IgM antibodies, 101
  anemia and, 401
  in biliary cirrhosis, 378
  complement activation and, 103
  hepatitis A (HAV), 170
  hyper-IgM syndrome, 113
  in pregnancy, 390
  in sclerosing cholangitis, 378
  splenic dysfunction, 94
IL-1 (Interleukin 1), 104
  cachexia and, 221
  endotoxins, 129
IL-2 (Interleukin 2), 104
  cyclosporine and, 116
  natural killer cells, effect on, 97
  sirolimus and, 116
  tacrolimus and, 116
IL-2R (Interleukin 2 receptor), 116
IL-3 (Interleukin 3), 104
IL-4 (Interleukin 4), 104
  helper T cells and, 98
IL-5 (Interleukin 5), 104
  helper T cells and, 98
IL-6 (Interleukin 6), 104
  acute-phase reactants and, 102
  cachexia and, 221
  endotoxins, 129
IL-8 (Interleukin 8), 104
  neutrophils and, 386
IL-10 (Interleukin 10), 104
  helper T cells and, 98
IL-12 (Interleukin 12), 104
  natural killer cells and, 97
  receptor deficiency, 112
IL-13 (Interleukin 13), 98
Ileum, 347
Ileus, 369
  gallstone, 379
Iliohypogastric nerve, 430
Illness anxiety disorder, 536
Iloperidone, 543
Iloprost, 648
Imatinib, 420
IMG registration timeframe, 6
Imipenem, 183, 186
  seizures with, 242
Imipramine, 545
Immature ego defenses, 525
Immature teratomas, 611
Immune responses, **102–115**
  acute-phase reactants, 97
  autoantibodies, 111
  cell surface proteins, 105
  complement, 103
  cytokines, 104
  hypersensitivity types, 110–111
  immunodeficiencies, 112–114
  passive vs active, 107
  respiratory burst, 105
  transfusion reactions, 110
Immune thrombocytopenia, 405
Immune thrombocytopenic purpura, 108
  hepatitis C, 169
Immunocompromised patients
  acyclovir/famciclovir/valacyclovir, 197
  Candida albicans in, 149
  common organisms affecting, 175
  Cryptococcus neoformans, 149
  Cryptosporidium, 151
  ecthyma gangrenosum, 139
  esophagitis in, 360
  fungal infections, 182
  Listeria monocytogens, 135
  Pneumocystis jirovecii, 150
Immunodeficiency
  infections in, 114
  syndromes, **112–113**
Immunodeficiency syndromes
  flow cytometry diagnosis, 50
Immunoglobins
  for Kawasaki disease, 302
Immunoglobulins
  adaptive immunity and, 95
  breast milk and, 599
  Guillain-Barré syndrome, 493
  isotypes of, **101**
Immunology, **92–118**
  immune responses, 102–115
  immunosuppressants, 116–118
  lymphocytes, 95–101
  lymphoid structures, 92–94
Immunomodulator signaling pathways, 322
Immunophenotype assessment, 50
Immunosuppressants, **116**
  for aplastic anemia, 399
  for lupus, 443
  for polymyositis/dematomyositis, 445
  targets, **117**
Immunosuppression
  squamous cell carcinoma, 454
  vitamin A deficiency, 62
  vitamin C deficiency, 65

- Impaired glucose tolerance. *See* Insulin resistance
- Impetigo, 447
  - crusts with, 451
  - *Streptococcus pyogenes*, 132
  - sunburn and, 453
- Implied consent, 254
- Imprinting (genetics), **54**
- Inactivated vaccines, 107
- Incidence vs prevalence, **249**
- Incomplete penetrance, **52**
- Incorrect results, in statistical hypothesis testing, 252
- Incus bone, 503
- Incus (ossicles)
  - branchial arch derivative, 587
- India ink stain, 122
- Indicator media, 122
- Indinavir
  - HIV therapy, **199**
  - mechanism (diagram), 197
- Indirect Coombs test, 108
- Indirect inguinal hernias, 355
- Indomethacin, 456
  - arachidonic acid pathway, 455
  - for diabetes insipidus, 334
  - gout, 440
  - for PDA closure, 270
- Infarcts
  - atherosclerosis, 292
  - red vs pale, 207
  - regions susceptible to, 206
- Inferior colliculi, 475
- Inferior gluteal nerve, 431
- Inferior mesenteric artery, 348
  - horseshoe kidney, 549
- Inferior mesenteric lymph nodes, 93
- Inferior mesenteric vein, 350
- Inferior oblique muscle, 510
- Inferior phrenic arteries, 348
- Inferior rectal artery, 351
- Inferior rectal vein, 350
- Inferior rectus muscle, 510
- Inferior sagittal sinus, 473
- Inferior vena cava, 345
  - diaphragm, 629
  - gonadal drainage and, 591
- Infertility
  - clomiphene, 621
  - cystic fibrosis, 56
  - ectopic pregnancy, 607
  - endometriosis, 613
  - impaired sperm mobility, 601
  - Kallmann syndrome, 604
  - Kartagener syndrome, 45, 656
  - Klinefelter syndrome, 603
  - leuprolide for, 621
  - mumps, 166
  - ovarian neoplasms, 610
  - PCOS, 609
  - salpingitis, 181
  - septate uterus, 590
  - varicoceles, 618
- Infiltrative cardiomyopathy, 297
- Infiltrative lymphohistiocytosis, 113
- Inflammation, **204–213**
  - acute-phase reactants, 102
  - characteristics of, **207**
  - ESR in, 212
  - IL-1 as cause, 104
  - pathology of, 204–213
- Inflammatory bowel disease (IBD), **365**
  - AA amyloidosis and, 213
  - azathioprine for, 417
  - erythema nodosum, 453
  - infliximab/adalimumab for, 457
  - methotrexate for, 417
  - sclerosing cholangitis and, 378
  - spondyloarthritis, 442
  - therapeutic antibodies, 118
- Inflammatory breast cancer, 616
- Inflammatory diseases
  - *Staphylococcus aureus*, 131
- Inflammatory pseudopolyps, 370
- Infliximab, 118, 457
  - for Crohn disease, 365
  - for ulcerative colitis, 365
  - ulcerative colitis, 664
- Influenza, **165**
  - antigenic variation, 106
  - orthomyxovirus, 163
  - pneumonia, 645
  - Reye syndrome and, 373
  - treatment/prevention, 197
  - vaccine for, 107, 158
- Informed consent, 254
- Infraspinatus muscle
  - Erb palsy, 428
  - rotator cuff, 425
- Infundibulopelvic ligament, 592
- Infundibulum, 474
- Ingested seafood toxins, **238**
- Inguinal canal, **354**
- Inguinal hernia, 355, 591
- Inguinal ligament, 353, 354
- Inguinal triangle, 355
- Inhalational general anesthetic, 244
- Inhalational injury, **640**
- Inhaled anesthetics, **519**
- Inheritance modes, **55**
- Inhibin
  - cryptorchidism, 617
  - Klinefelter syndrome, 603
  - Sertoli cell secretion of, 594
- Inhibin A
  - autosomal trisomies, 59
- Inhibitors of complement activation, 103
- Inhibitory pathway, 470
- Initiation of protein synthesis, 41
- Innate immunity, **95**
- Inositol trisphosphate (IP$_3$), 322
- Inotropes, 299
- Inotropy, 275
- Insomnia
  - AChE inhibitors, 518
  - barbiturates for, 515
  - benzodiazepines, 515
  - hyperthyroidism and, 327
  - marijuana withdrawal, 541
  - nonbenzodiazepine hypnotics, 515
  - stimulants causing, 540
- Inspiration effect on auscultation, 278
- Inspiratory capacity (IC), 630
- Inspiratory reserve volume (IRV), 630
- Insulin, **314**
  - anabolic effects of, 314
  - deficiency in, 336
  - diabetes treatment, 340
  - diabetic ketoacidosis, 337
  - for HHNS, 338
  - fructose bisphosphatase-2 and, 72
  - GIP effect on, 356
  - glucagon and, 315
  - glycogen regulation, 69, **81**
  - hypokalemia from, 560
  - in pregnancy, 314
  - production of, 313
  - secretion of, 314
  - signaling pathways for, 322
  - somatostatin and, 356
  - somatostatinomas and, 338
  - sulfonylurea effect on, 340
- Insulin-like growth factor 1 (IGF-1)
  - acromegaly, 333
  - Laron syndrome, 333
  - signaling pathways for, 322
- Insulinomas
  - insulin and C-peptide in, 314
  - MEN 1 syndrome, 339
  - pancreatic cell tumor, **338**
- Insulin resistance
  - acanthosis nigricans and, 453
  - acromegaly, 333
  - cortisol, 319
  - Cushing syndrome, 323
  - DM type 2, 337
  - GH, 314, 317
  - glitazone/thiazolidinedione effect on, 340
  - metformin effect on, 340
  - PCOS, 609
- Insurance
  - disregarding in treatment, 257
  - Medicare/Medicaid as, 260
  - types of plans, 259
- Integrase inhibitors, 199
- Integrins
  - epithelial cells, 447
  - viral, receptor, 162
- Intellectual disabilities
  - WAGR complex, 569
- Intellectual disability
  - autism and, 527
  - fetal alcohol syndrome, 583
  - Rett syndrome, 527
- Intellectualization, 525
- Intention tremor, 489
  - cerebellar lesions, 481
  - multiple sclerosis, 493
- Intention tremors
  - multiple sclerosis, 655
- Interactions, drug, **225**
- Intercostobrachial nerve, 427
- Interferon-α
  - myopathy, 241
- Interferon-γ release assay (IGRA), 136
- Interferons, 105
  - focal segmental glomerulosclerosis, 566
  - mechanism and use, **200**
- Interlobar artery, 550
- Interlobular artery, 550
- Intermediate filaments
  - cytoskeletal element, 44
- Internal auditory meatus, 476
- Internal capsule
  - intraparenchymal hemorrhage, 483
  - stroke effects, 484
- Internal carotid artery
  - cavernous sinus, 512
  - circle of Willis, 473
- Internal hemorrhoids, 351
- Internal iliac arteries, 348
- Internal iliac artery, 270
- Internal iliac lymph nodes, 93, 591
- Internal inguinal ring, 355
- Internal jugular vein, 473
- Internal oblique muscle, 354
- Internal spermatic fascia, 354
- International Foundations of Medicine (IFOM), 12
- Internuclear ophthalmoplegia, **513**
  - multiple sclerosis, 655
- Interossei muscles, 429
  - Klumpke palsy, 428
  - ulnar nerve, 427
- Interpreting study results, 250
- Intersex, 604
- Interstitial fluid, 287
- Interstitial lung disease, 439
- Interstitial nephritis
  - as drug reaction, 242
  - NSAID toxicity, 456
  - penicillins, 184
- Interstitial pneumonia, 645
- Interstitium
  - leukocyte extravasation and, 209
- Interventricular foramen, 269
- Interventricular septal rupture, 296
- Intestinal obstruction
  - hernias as cause, 355
  - superior mesenteric artery syndrome as cause, 348
- Intestinal stomach cancer, 362
- Intestinal villi, 347
- Intimate partner violence, 257
- Intracellular fluid (ICF), 551
- Intracellular organisms, **124**
- Intracellular receptors
  - endocrine hormone messengers, 322
- Intracranial hemorrhage, **483**
  - eclampsia, 608
- Intracranial pressure, 472
  - hydrocephalus, 492
  - papilledema, 508
  - superior vena cava syndrome, 646
- Intraductal papillomas, 614, 615
- Intraocular pressure, 506
- Intraparenchymal hemorrhage, 483
- Intrauterine device (IUD)
  - copper, 622
  - endometritis, 612
- Intrauterine growth restriction (IUGR)
  - low birth weight, **599**
  - substance abuse, 582

Intravascular hemolysis, 399
Intravenous anesthetics, **519**
Intraventricular hemorrhage
  low birth weight, 599
  neonatal respiratory distress syndrome as cause, 627
Intrinsic factor, 357
  location of, 357
Intrinsic hemolytic anemia, **400**
Intrinsic pathway, **204**
  for coagulation, 391
  coagulation defects of, 404
  heparin and, 414
Intrinsic renal failure, 571
Introns vs exons, **39**
Intrusive thoughts, 533
Intussusception, **368**
  Meckel diverticulum as cause, 367
  presentation, 655
Inulin
  extracellular volume and, 551
  glomerular filtration rate and, 552
  in proximal convoluted tubules, 557
Invariant chain, 96
Invasive breast carcinomas, 616
Invasive carcinomas, 215
In vivo biofilm-producing bacteria, **125**
Involuntary treatment, 255
Iodine
  deficiency in, 327, 328
  infection control, 200
  teratogenicity, 582
  thionamide effect on, 341
Iodophors, 200
IPEX syndrome, 98
Ipratropium, 233, 649
Irinotecan, **419**
  in cell cycle, 416
  targets of, 416
Irinotecan/topotecan, 35
Iris, 504
Iritis, 506
Iron
  absorption of, 358
  anemia, 402
  anemia of chronic disease, 399
  in hemochromatosis, 378
  lab values in anemia, 402
  metabolic acidosis, 561
  sideroblastic anemia, 397
  toxicity treatment, 239
Iron deficiency anemia, 396
  in anemia taxonomy, 396
  colorectal cancer as cause, 371
  fibroid tumors, 612
  Plummer-Vinson syndrome as cause, 360
Iron poisoning, **404**
Irritable bowel syndrome (IBS), **366**
  antispasmodic drugs, 233
Ischemia, **206**, 634
  atherosclerosis, 292
  Fanconi syndrome, 556
  necrosis and, 205
Ischemic brain disease, **482**
Ischemic heart disease, **293**
Ischemic priapism, 617
Ischemic stroke, **482**
Ishikawa diagram, 262
Islets of Langerhans, 313
Isocarboxazid, 546
Isocitrate dehydrogenase
  metabolic pathways, 70
  rate determining enzyme, 69
Isodisomy, 53
Isoflurane, 519
Isolation of affect, 525
Isoleucine
  classification of, 77
  maple syrup urine disease and, 80
Isoniazid, **193**
  cytochrome P-450, 243
  drug-induced SLE, 657
  hemolysis in G6PD deficiency, 241
  hepatitis, 240
  lupus-like syndrome, 241
  Mycobacterium tuberculosis, 192
  seizures, 242
  sideroblastic anemia, 397
Isoproterenol
  norepinephrine vs, **235**
  sympathomimetic action, 234
Isosorbide dinitrate, 305
Isosorbide mononitrate, 305
Isotretinoin
  cystic acne, 62
  teratogenicity, 582
Isovolumetric contraction, 276
Isovolumetric relaxation, 276
Isuccinate dehydrogenase, 74
Itraconazole
  azoles, 195
  mechanism (diagram), 194
  Sporothrix schenckii, 150
  systemic mycoses, 147
Ivabradine, 310
IV drug use
  common organisms, 175
  osteomyelitis, 176
Ivermectin, 196
IV phlebitis, 195
Ixodes ticks, 142, 144, 153

J

JAK2 gene, 218
  myeloproliferative disorders, 411
Janeway lesions, 655
  bacterial endocarditis, 299
Jarisch-Herxheimer reaction, **143**
Jaundice, **376**
  ABO hemolytic disease of the newborn, 390
  alcoholic cirrhosis as cause, 374
  biliary tract disease as cause, 378
  cholangitis as cause, 379
  cirrhosis as cause, 372
  Crigler-Najjar syndrome, 656
  as drug reaction, 240
  fructose intolerance, 76
  galactosemia, 76
  graft-versus-host disease, 115
  hepatitis B, 180
  hepatocellular carcinoma as cause, 375
  hereditary hyperbilirubinemias as cause, 377
  leptospirosis, 142
  painless, 656
  pancreatic cancer as cause, 380
  ToRCHeS infections, 178
  yellow fever, 164
Jaw jerk reflex, 477
JC virus (John Cunningham virus)
  HIV-positive adults, 173
  polyomaviruses, 160
  progressive multifocal leukoencephalopathy and, 494
JC virus (John Cunningham Virus)
  immunocompromised patients, 114
Jejunum, 347
Jervell and Lange-Nielsen syndrome, 283
Jimson weed, 233
Jod-Basedow phenomenon, 329. *See also* Wolff-Chaikoff effect
JONES criteria (rheumatic fever), 132
J point in ECG, 282
Jugular foramen, 473, 476
Jugular venous distention (JVD), 298, 646
Jugular venous pulse, 276
Justice (ethics), 253
Juvenile idiopathic arthritis, 506
Juvenile polyposis, 370
Juxtaglomerular apparatus, **558**
  filtration, 553
  juxtaglomerular cells, 550
  renin secretion, 558
Juxtaglomerular cells
  tumors in, 324

K

Kallikrein
  C1 esterase inhibitor deficiency, 103
  neutrophils and, 386
Kallmann syndrome, **604**
Kaposi sarcoma, 450
  AIDS and, 180
  bacillary angiomatosis vs, 450
  HHV-8, 161
  HIV-positive adults, 173
  IFN-α for, 200
  oncogenic microbes and, 219
  recombinant cytokines for, 117
Kartagener syndrome, 45, 268
  infertility with, 601
  obstructive lung disease, 639
  presentation, 656
Karyotyping, **51**
Kawasaki disease, **302**
  presentation, 652, 656
Kayser-Fleischer rings
  Wilson disease as cause, 378
K cells, 356
Kegel exercises, 569
Keloid scars, 210
Keratinocytes
  sunburn, 453
  in wound healing, 211
Keratin pearls, 647
Keratoacanthomas, 454
Keratoconjunctivitis, 160
Keratoconjunctivitis sicca, 441
Keratomalacia, 62
Kernicterus, 190, 201
Kernohan notch, 499
Ketamine, 519
Ketoconazole, 194, 195, 623
  cytochrome P-450, 243
  gynecomastia, 615
  PCOS, 609
  reproductive hormones and, 620
Ketogenesis
  diabetic ketoacidosis, 337
  diagram of, 70
  insulin deficiency, 336
  metabolic site, 68
  rate-determining enzyme for, 69
Ketone bodies, **86**
Ketonemia, 336
Ketonuria, 336
Ketorolac, 456
  arachidonic acid pathway, 455
Kidney
  chronic graft nephropathy, 115
  transplant prophylaxis, 116
Kidney disease
  anemia of chronic disease and, 399
  hypertension, 290
Kidney endocrine functions, **559**
Kidneys
  autoregulation of, 286
  embryologic derivation, 581
  embryology of, **548**
  in gastrointestinal anatomy, 345
  hormones acting on, **559**
  ischemia in, 206
  sclerosis, 446
  solitary functioning, 549
Kidney stones, **567**
  Crohn disease as cause, 365
  electrolyte disturbances, 560
  hematuria with, 562
  horseshoe kidney and, 549
  hydronephrosis, 568
  hyperparathyroidism, 332
  postrenal azotemia, 571
  UTIs, 177
Kiesselbach plexus, 636
Killed vaccines, 158
Killian triangle, 367
Kimmelstiel-Wilson nodules
  diabetes mellitus, 336
  diabetic glomerulonephropathy, 566
Kinases, 69
Kinesin, 44
Kingella spp, 299
Kinin cascade, 391
Kinin pathways, **391**
kinky hair, 47
Kissing bug (disease vector), 154

Klebsiella spp, **140**
  alcoholism, 175
  currant jelly sputum, 182
  Gram-negative algorithm, 137
  kidney stones, 567
  lactose fermentation, 138
  nosocomial infections, 181
  pneumonia, 645
  taxonomy, 121
  urease-positive, 124
  urinary tract infections, 570
Klebsiella pneumoniae
  cephalosporins, 185
  encapsulation, 124
  immunodeficient patients, 114
  presentation, 655
  splenic dysfunction, 94
  UTIs caused by, 177
Klinefelter syndrome, 603
  chromosome association, 60
  gynecomastia, 615
  testicular tumors, 618
Klumpke palsy, 428
Klüver-Bucy syndrome, 481
Knee pain from "unhappy triad," 425
Knees
  common conditions of, **425**
  examination of, **424**
Knock-out/Knock-in genes, 52
Koilocytes, 609
  condylomata acuminata, 180
Koilocytosis, 449
Koplik spots, 166, 179, 656
Korsakoff psychosis, 541
Korsakoff syndrome, 528
Krabbe disease, 84, 494
KRAS gene, 218
  adenomatous colonic polyps and, 370
  colorectal cancer and, 372
  lung cancer and, 647
Krukenberg tumor, 611
Krukenberg tumors, 362
K_m, 224
Kulchitsky cells, 325, 647
Kupffer cells, 352
Kuru, 174
Kussmaul respirations
  in diabetic ketoacidosis, 337
Kussmaul sign, **301**
Kwashiorkor, **67**
Kyphoscoliosis, 501
Kyphosis, 80

L

Labetalol, 237
  gestational hypertension, 608
  hypertension in pregnancy, 304
  hypertensive emergency, 304
Labia, 592
  male homolog of, 590
Labile cells, 42
Laboratory techniques, **48–52**
Lachman test, 424
Lac operons, **36**
Lacrimation reflex, 477
Lactase deficiency, **77**
Lactation, **599**. *See also* Breast milk
  dopamine and, 316
  oxytocin for, 342
  progesterone and, 595
  prolactin and, 316
  Sheehan syndrome and, 335
Lactational mastitis, 615
Lactic acid dehydrogenase, 73
Lactic acidosis
  ethanol metabolism and, 68
  exercise and, 635
  MELAS syndrome, 55
  metabolic acidosis, 561
  metformin, 340
  pyruvate dehydrogenase complex deficiency, 73
Lactiferous sinus, 614
Lactobacillus spp
  normal flora, 174
  taxonomy, 121
Lactoferrin
  in neutrophils, 386
  in respiratory burst, 105
Lactose-fermenting enteric organisms, 123, **138**
Lactose intolerance, 364
Lactose metabolism, 36
Lactulose, 383
  for hepatic encephalopathy, 374
  hyperammonemia, 78
Ladd bands, 367
Lambert-Eaton myasthenic syndrome, **445**
  as paraneoplastic syndrome, 217
  small cell lung cancer, 647
Lamina propria, 347
  Peyer patches in, 358
  in Whipple disease, 364
Lamins, 44
Lamivudine
  HIV therapy, 199
  mechanism (diagram), 197
Lamotrigine
  for epilepsy, 514
  rash caused by, 241
Lancet-shaped diplococci, 132
Landmark dermatomes, **480**
Langerhans cell histiocytosis, **412**
Langerhans cells, 388
  Birbeck granules in, 660
Language development, 258
Lanosterol synthesis, 194
Lansoprazole, 381
Lanugo, 537
Laplace law, 273, 627
Large cell carcinomas of lungs, 647
Laron syndrome, **333**
Larva migrans, 155
Larynx, 628
Larynx muscles, 587
Lassa fever encephalitis, 163
Latent errors, 262
Lateral cerebellar lesions, 469
Lateral collateral ligament (LCL) injury, 424
Lateral corticospinal tract, 478, 479, 484
Lateral epicondylitis, 426
Lateral femoral circumflex artery, 436
Lateral femoral cutaneous nerve, 430
Lateral fold closure defects, 344
Lateral geniculate nucleus (LGN), 468
Lateral medullary syndrome, 484
Lateral pterygoid muscle, 587
Lateral rectus muscle, 510
Lateral spinothalamic tract, 478
Lateral thoracic artery, 432
Lateral ventricles
  herniation syndromes, 499
  optic radiation, 511
  ventricular system, **474**
Laxatives, 383
LDH in exudate vs transudate, 212
LDL (low-density lipoprotein), 89
Leaden paralysis, 531
Lead poisoning, 397, **403**
  acute tubular necrosis, 572
  in anemia taxonomy, 396
  basophilic stippling in, 394
  Fanconi syndrome, 556
  labs/findings, 657
  presentation, 652
  sideroblastic anemia, 397
  treatment, 239
Lead-time bias, 250
Lecithinase, 129, 134
Lecithin-cholesterol acetyltransferase)
  activation of, 89
  function, 88
lecithins
  lung maturity, 627
Lecithins, 627
Lectin pathway (complement activation), 103
Ledipasvir, 200
Leflunomide, 439, **456**
  pyrimidine synthesis and, 33
Left anterior descending artery
  coronary circulation, 271
  myocardial infarction and, 294
Left anterior division, 282
Left bundle branch, 282
Left bundle branch block, 277
Left circumflex coronary artery, 271
Left common iliac artery, 348
Left gastroepiploic artry, 349
Left hamianopia with macular sparing, 511
Left heart disease, 643
Left horn of sinus venosus, 268
Left lower quadrantic hemiopia, 511
Left main coronary artery, 271
Left marginal artery, 271
Left posterior division, 282
Left recurrent laryngeal nerve, 586
Left shift, **402**
Left-to-right shunts, 289
Legg-Calvé-Perthes disease, 436
Legionella spp
  atypical organism, 175
  culture requirements, 123
  ntracellular organism, 124
  macrolides, 189
  nosocomial infection, 181
  pneumonia, 645
  silver stain, 122
  taxonomy, 121
Legionella pneumophila, **139**
Legionnaires' disease, 139
Leiomyomas, 612
  nomenclature for, 216
  polycythemia and, 217
Leiomyosarcomas, 216
Leishmania donovani, **154**
Leishmaniasis, 154, 196
Lens, 504
  collagen in, 46
  infantile cataracts, 76
  subluxation of, 80
Lenticulostriate artery, 484
Lentiform nucleus, 470
Leonine facies, 137
Lepromatous Hansen disease, 137
Leptin, 317
  hypothalamus, 466
Leptospira spp
  animal transmission, 144
  spirochete, 142
Leptospira interrogans, **142**
Leptospirosis, 142, 144
Lesch-Nyhan syndrome, **34**
  gout, 440
  inheritance, 56
  labs/findings, 660
Leser-Trélat sign, 217, 449
  stomach cancer as cause, 362
Lesser sac, 346
Lethal median dose, 228
Letrozole, 621
Leucine
  classification of, 77
  maple syrup urine disease and, 80
Leucovorin, 417
Leukemias, **410**
  allopurinol for, 457
  aplastic anemia and, 399
  carcinogens causing, 219
  cyclophosphamide for, 418
  cytarabine for, 417
  doxorubicin for, 418
  etoposide/teniposide for, 419
  lymphomas vs, **407**
  mucormycosis, 149
  nomenclature for, 216
  vinca alkaloids for, 419
Leukocyte adhesion deficiency, 113, 209
Leukocyte alkaline phosphatase (LAP), 386
Leukocyte esterase, 177, 570
Leukocyte extravasation, **209**
Leukocytes, **386**
  basophilia in CML, 387
  extravasation of, 209
  leukemias, 410
  in urine, 177, 562, 570
Leukocytoclastic vasculitis, 169

Leukocytosis
  Clostridium difficile, 652
  diabetic ketoacidosis, 337
  nosocomial infections, 181
Leukodystrophies, 464, 494
Leukopenia, **402**
  cytarabine, 417
  ganciclovir, 198
  immunosuppressants and, 116
  trimethroprim, 190
Leukoplakia, 451
Leukotriene receptor antagonists, 455
Leukotrienes, 455
  basophils and, 387
  cortisol effects, 319
Leuprolide, **621**
Levator veli palatin muscle, 587
Levetiracetam, 514
  tonic-clonic seizures, 663
Levodopa, 517, **518**
Levofloxacin
  fluroquinalones, 191
  mechanism (diagram), 183
  Pseudomonas aeruginosa, 139
Levomilnacipran, 545
Levornorgestrel, 622
Levothyroxine, **342**. *See also* Thyroid hormones
Lewy bodies, 490
Lewy body dementia, 490, 529
Leydig cells
  cryptorchidism, 617
  endocrine function, 594
  genital embryology, 589
  tumors, 619
LFA-1 antigens, 209
LH. *See* Luteinizing hormone (LH)
Libido
  in geriatric patients, 259
  testosterone and, 600
Libman-Sacks endocarditis, 443
Lice
  disease vectors, 144, 145
  head/scalp, 157
  treatment, **196**
Lichen planus, 169, 448, 453
  presentation, 655
Liddle syndrome, **556**
  markers in, 560
Lidocaine, 308, 519
  arrhythmia, 661
Life support
  withdrawal, 257
Li-Fraumeni syndrome
  osteosarcomas, 438
  tumor suppressor genes in, 218
Ligaments, gastrointestinal, **346**
Ligamentum arteriosum, 270
Ligamentum teres hepatis, 270, 346
Ligamentum venosum, 270
Ligand receptors, 204
Light criteria, 212
Likelihood ratio (LR), 247
Limbic system, **468**
Limit dextrin, 82
Limited scleroderma, 446
Linagliptin, 341
Lindane, 196
Linea alba, 354
Linear ulcers, in esophagitis, 360
Linear viruses, 159
Lines of Zahn, 637, 660
Lineweaver-Burk plot, 224
Linezolid, **189**
  highly resistant organisms, 194
  mechanism (diagram), 183
  protein synthesis inhibition, 187
Linkage disequilibrium, 52
Lipase
  as pancreatic secretions, 358
  in pancreatitis, 380
Lipid-lowering agents, **306**
Lipids
  metabolism of, 70
  transport of, **88**
  viral structure, 158
Lipodystrophy
  insulin and, 340
  protease inhibitors, 199
  tesamorelin for, 315
Lipofuscin, **213**
Lipoic acid, 72
Lipoid nephrosis, 566
Lipolysis
  cortisol and, 319
  insulin and, 314
  in insulin deficiency, 336
  niacin and, 306
  sympathetic receptors and, 230
  thyroid hormones and, 321
Lipomas, 216
Lipoprotein lipase, 88
Lipoproteins, **89**
Liposarcomas, 216
Lipoteichoic acid, 120
Liquefactive necrosis, 205
Liraglutide, 341
Lisch nodules
  neurofibromatosis, 495, 652
Lisinopril, 577
Lispro insulin, 340. *See also* Insulin
Listeria spp
  catalase-positive organism, 124
  Gram-positive algorithm, 130
  intracellular organism, 124
  meningitis, 176
  taxonomy, 121
Listeria monocytogenes, **135**
  β-hemolysis, 131
  granulomatous diseases, 211
  neonates, 178
  penicillins for, 184
Lithium, **544**
  for bipolar disorder, 531, 661
  diabetes insipidus and, 334, 240
  hypothyroidism, 240, 328
  prenatal exposure, 288, 290
  teratogenicity, 582
  therapeutic index value of, 228
Live attenuated vaccines, 107, 158
Livedo reticularis, 517
Liver
  blood supply and innervation of, 348
  in gastrointestinal anatomy, 346
  ischemia in, 206
  lipid transport and, 88
  as metastasis site, 221
  tissue architecture, **352**
Liver disease
  acanthocytes in, 394
  alcoholic, 374
  anemia, 398
  in anemia taxonomy, 396
  cystic fibrosis, 56
  echinocytes in, 394
  labs/findings, 660
  loading and maintenance dose in, 225
  target cells in, 395
Liver failure
  Budd-Chiari syndrome and, 375
  movement disorder in, 489
  Wilson disease as cause, 378
Liver fluke
  hyperbilirubinemia caused by, 376
  as oncogenic microbe, 219
Liver pathology serum markers, **373**
Liver tumors, **375**
Living wills, 255
Lleukoerythroblastic reaction, 402
LMN facial nerve palsy
  presentation, 656
Loading dose, 225, 669
Loa loa, 154, 155
Lobar pneumonia, 643, 645
Lobular carcinomas, 614
Local anesthetics, **519**
  naming convention, 244
Locked-in syndrome
  basilar artery lesions, 485
  osmotic demyelination syndrome, 492
Lockjaw
  Clostridium tetani, 134
  tetanospasmin, 128
Locus heterogeneity, **53**
Löffler medium, 123
Löffler syndrome, 297
Lomustine, 418
  in cell cycle, 416
Lone Star tick (disease vector), 144
Long QT syndrome
  ranolazine, 305
  sudden cardiac death, 293
Loop diuretics, **575**
  for heart failure, 298
  metabolic alkalosis, 561
  site of action, 574
  toxicity of, 242
Loop of Henle, 574
Loperamide, **382**, 520
Lopinavir
  HIV therapy, 199
  mechanism (diagram), 197
Loratadine, 648
Lorazepam, 515
  alcohol withdrawal, 542
Losartan, 577
Lou Gehrig disease, 500
Lovastatin, 306
Low birth weight, **599**
Löwenstein-Jensen agar, 123
Lower esophageal sphincter
  achalasia and, 360
  in Barrett esophagus, 361
Lower extremity nerves, **430**
Lower left quadrant (LLQ) pain, 366
Lower motor neuron (LMN) lesions, 501, 502
LPS endotoxin, 120, 127, 129, 140
LTB$_4$ (Leukotriene B4), 386, 455
Lumbar puncture, 478, 491
Lumbosacral radiculopathy, **432**
Lumbrical muscles, 429
  Klumpke palsy and, 428
  median and ulnar nerves, 427
Lumefantrine, 196
Lunate bone, 426
Lung abscesses, **646**
Lung and chest wall expansion, **631**
Lung cancer, **647**
  apical tumor, 657
  asbestosis and, 641
  carcinogens causing, 219
  cisplatin/carboplatin for, 419
  eriotinib for, 420
  hypercalcemia and, 217
  incidence/mortality in, 216
  metastases of, 221
  neuromuscular paraneoplastic syndromes and, 217
  oncogenes and, 218
  SIADH, 668
  topotecan for, 419
Lung diseases
  obstructive, **638**
  restrictive, **639**
Lungs
  anatomical relationships, **629**
  autoregulation of, 286
  development of, **626**
  physical findings, **643**
  sclerosis of, 446
Lung volumes, **630**
Lupus, **443**
  acute interstitial nephritis, 572
  anemia of chronic disease and, 399
  antiphospholipid syndrome, 443
  autoimmune hemolytic anemia and, 401
  azathioprine for, 417
  bacterial endocarditis, 299
  DPGN, 564
  HLA subtypes, 96
  isoniazid, 193
  lab/findings, 661
  lymphopenia, 402
  membranous nephropathy, 566
  microangiopathic anemia, 401
  neutropenia, 402
  presentation, 652
  Raynaud phenomenon, 445

- Lupus-like syndrome
  - α-methyldopa, 235
  - as drug reaction, 241
  - hydralazine, 304
  - procainamide, 308
- Lupus nephritis, 443
- Lupus pernio, 444
- Lurasidone, 543
- Luteal phase, 597
- Luteal phase of menstrual cycle, 597
- Luteinizing hormone (LH)
  - clomiphene effect, 621
  - contraception, 622
  - cryptorchidism, 617
  - estrogen/progesterone, 595
  - hCG and, 584, 618
  - Klinefelter syndrome, 603
  - leuprolide, 621
  - menopause, 600
  - ovulation, 316, 596
  - PCOS, 609
  - pharmacologic control of, 620
  - premature ovarian failure, 609
  - secretion of, 313
  - sex development disorders, 604
  - signaling pathways of, 322
  - spermatogenesis, 316, 594
  - testosterone, 623
  - Turner syndrome, 603
- Lyme disease, **142**
  - animal transmission, 144
  - AV block in, 284
  - ceftriaxone, 185
- Lymphadenopathy
  - bilateral hilar, 639
  - *Corynebacterium diphtheriae*, 128, 135
  - follicular lymphoma, 408
  - Kawasaki disease, 652
  - Lymphogranuloma venereum, 180
  - mononucleosis, 161
  - rubella, 165, 178, 179
  - serum sickness, 109
  - syphilis, 143, 180
  - tinea capitis, 148
  - *Toxoplasma gondii*, 178
  - *Trypanosoma brucei*, 152
- Lymphatic gonadal drainage, 591
- Lymphatic pleural effusion, 644
- Lymphatic regional drainage, 93
  - deep inguinal nodes, 591
  - external iliac nodes, 591
  - gonadal drainage, 591
  - internal iliac nodes, 591
  - malignant breast tumors, 616
  - para-aortic lymph nodes., 591
  - superficial inguinal nodes., 591
- Lymphedema, 603, 656
- Lymph nodes, **92**
  - absent or scanty, 112
  - T cell differentiation, 97
  - TNM tumor staging, 216
  - tumor metasases, 221
- Lymphocyte-depleted lymphoma, 407
- Lymphocyte-rich lymphoma, 407
- Lymphocytes, **95–100**, **388**
  - breast milk and, 599
  - CLL/small cell lymphocytic lymphoma, 410
  - corticosteroid effect on, 402
  - lymph nodes, **92**
  - non-Hodgkin lymphoma, 408
  - spleen, 94
  - thymus, 94
- Lymphocytic choriomeningitis virus (LCMV), 163
- Lymphocytosis, 94
- Lymphogranuloma venereum, 146, 180
- Lymphohistiocytosis, 113
- Lymphoid hyperplasia, 366
- Lymphoid structures, **92–93**
- Lymphomas
  - allopurinol, 457
  - associations, 668
  - carcinogens causing, 219
  - celiac disease and, 364
  - cyclophosphamide for, 418
  - cytarabine for, 417
  - doxorubicin for, 418
  - EBV and, 161
  - etoposide/teniposide for, 419
  - hypercalcemia and, 217
  - leukemias vs, **407**
  - methotrexate for, 417
  - minimal change disease, 566
  - nomenclature for, 216
  - non-Hodgkin, 407, 408
  - oncogenic microbes, 219
  - of stomach, 362
  - thyroiditis association with, 330
- Lymphopenias, 402
  - ataxia-telangiectasia, 113
  - corticosteroid effect on, 402
- Lynch syndrome, 371
  - endometrial cancer, 612
  - mismatch repair and, 37
  - ovarian neoplasms, 610
- Lysergic acid diethylamide (LSD), 541
- Lysine
  - classification of, 77
  - in cystinuria, 81
  - kidney stones, 567
  - for pyruvate dehydrogenase complex deficiency, 73
- Lysosomal α-1,4-glucosidase, 83
- Lysosomal storage diseases, 43, **84**
- Lysozyme
  - innate immunity, 95
  - in neutrophils, 386
- *LYST* gene, 113
- Lysyl oxidase, 47
- Lytic bone lesions
  - adult T-cell lymphoma, 408
  - Langerhans cell histiocytosis, 412
  - multiple myeloma and, 409

M

- MacConkey agar, 122, 123, 138
- Macroangiopathic anemia, 396, 401
- Macrocytic anemia, 396, **398**
- Macroglossia, 569
- Macrolides, **189**
  - cytochrome P-450 and, 243
  - hypertrophic pyloric stenosis and, 345
  - *Legionella pneumophila*, 139
  - mechanism (diagram), 183
  - *Mycoplasma pneumoniae*, 146
  - naming convention for, 244
  - protein synthesis iinhibition, 187
  - torsades de pointes, 239
- Macroorchidism, 58
- Macro-ovalocytes, 394
- Macrophages, **387**
  - alveolar, 628
  - apoptosis and, 204
  - bilirubin and, 359
  - binding of, 100
  - breast milk and, 599
  - cell surface proteins, 106
  - in chronic inflammation, 207
  - cytokine secretion, 104
  - endotoxin activation, 129
  - endotoxins/lipopolysaccharide, 106
  - innate immunity, 95
  - in lymph node, 92
  - lymphocyte interaction, 98
  - in MI, 294
  - necrosis and, 205
  - pneumoconioses, 641
  - in spleen, 94
  - in wound healing, 211
- Macrosomia, 582
- Macula densa, 550
  - filtration and, 553
  - juxtaglomerular apparatus, 558
- Macular cherry-red spot, 84, 507, 652
- Macular degeneration, **506**
- Macules, 447
- Maculopapular rash
  - graft-versus-host disease, 115
  - rubeola, 166
  - syphilis, 143
- Magnesium
  - antiarrhythmic treatment, 310
  - cardiac glycoside toxicity, 307
  - proton pump inhibitor effect on, 381
  - PTH regulation, 320
  - in renal disorders, 560
  - torsades de pointes and, 283
- Magnesium citrate, 383
- Magnesium hydroxide, 382, 383
- Magnesium sulfate
  - preeclampsia/eclampsia, 608
- Maintenance dose, 225, 669
- Maintenance stage, 539
- Major basic protein (MBP), 387
- Major depressive disorder, 530, **531**
  - tricyclic antidepressants, 545
- Major ducts (breast), 614
- Malabsorption syndromes, **364**, 365
  - fat-soluble vitamin deficiencies, 61
  - osteoporosis, 435
- Malaria
  - anemia in, 401
  - artesunate for, 196
  - *Plasmodium*, 153
  - quinidine/quinine for, 196
- *Malassezia* spp, 148
- Malathion, 196
- Male genital embryology, 589
- Male reproductive anatomy, **593**
- Male sexual response, 593
- Maleylacetoacetic acid, 79
- Malignant hypertension
  - microangiopathic anemia, 401
  - RBC casts in, 562
- Malignant hyperthermia, 519, 520
- Malignant melanomas
  - IFN-α for, 200
  - recombinant cytokines, 117
- Malignant mesotheliomas, 220
- Malignant tumors, 216
- Malingering, **536**
- Malleus, 503
- Malleus (ossicles), 587
- Mallory bodies
  - in alcoholic hepatitis, 374
- Mallory-Weiss syndrome, 360, 656
- Malnutrition, **67**
  - superior mesenteric artery syndrome and, 348
- Malrotation, **367**
- Maltese cross appearance, 153
- "Maltese cross" sign, 562
- MALT lymphomas
  - *Helicobacter pylori*, 142
  - oncogenic microbes and, 219
  - Sjögren syndrome, 441
- Mammary glands, 581
- Mammillary bodies, 468, 474, 481
  - Korsakoff syndrome, 528
  - Wernicke-Korsakoff syndrome, 541
- Mandibular process, 587
- Mango flies (disease vector), 155
- Manic episodes, **530**
- Mannitol, **575**
  - extracellular volume and, 551
  - site of action, 574
- Mantle cell lymphoma, 408, 412
  - chromosomal translocations and, 412
- Mantle zone
  - lymph nodes, 92
  - spleen, 94
- MAO inhibitors, **546**
  - atypical depression, 531
  - mechanism of, 544
  - Parkinson disease, 517
  - phobias, 533
  - selegiline/rasagiline, 518
  - serotonin syndrome, 545
  - tyramine and, 236
- Maple syrup urine diseae, **80**
- Marantic endocarditis, 217
- Marasmus, **67**
- Maraviroc, 197, 199
- Marburg hemorrhagic fever, 163
- Marcus Gunn pupils, **509**
  - multiple sclerosis, 493
- Marfanoid habitus
  - homocystinuria, 80
  - MEN 2B syndrome and, 339

- Marfan syndrome
  - aortic aneurysms, 664
  - aortic dissection and, 293
  - cardiac defect association, 290
  - cataracts, 505
  - chromosome association, 60
  - elastin and, 48
  - heart murmur with, 279
  - presentation, 652
  - thoracic aortic aneurysms and, 292
- Marginal zone lymphoma, 408
- Marijuana
  - intoxication and withdrawal, 541
  - schizophrenia and, 530
- Masseter muscle, 587
- Massive hepatic necrosis, 240
- Mast cells, **387**
  - IgE antibody and, 101
- Mastectomy and winged scapula, 428
- Mastication muscles, **477**
- Mastitis, 614
- Mastoid air cells, 588
- Mastoiditis
  - brain abscesses, 176
  - Wegener granulomatosis, 302
- Maternal diabetes
  - cardiac defect association, 290
- Maternal-fetal placental barrier, 466
- Maternal PKU, 80
- Mature cystic teratomas, 610
- Mature ego defenses, 525
- Maxillary artery, 586
- Maxillary process, 587
- Mayer-Rokitansky-Küster-Hauser syndrome, 589
- McArdle disease, 83
- McBurney point, 366
- McBurney sign, 656
- McCune-Albright syndrome, 53, 652
- McMurray test, 424
- MDMA (ecstasy), 541
- Mean, 251
- Mean arterial pressure, 272, 472, 669
- Measles, **166**, 179
  - paramyxovirus, 163, 165, 166
  - presentation, 656
  - unvaccinated children, 182
  - vaccine, 107, 158
  - vitamin A for, 62
- Measurement bias, 250
- Measures of central tendency, 251
- Measures of dispersion, 251
- Mebendazole, 196
  - microtubules and, 44
- "Mechanic's hands" in dermatomyositis, 445
- Meckel diverticulum, **367**, 585
- Meconium ileus, 369
  - cystic fibrosis, 56
- *MECP2*, 527
- Medial antebrachial cutaneous nerve, 427
- Medial brachial cutaneous nerve, 427
- Medial calcific sclerosis, 291
- Medial cerebellar lesions, 469
- Medial collateral ligament (MCL) injury
  - abnormal passive abduction in, 424
  - in "unhappy triad," 425
- Medial epicondylitis, 426
- Medial femoral circumflex artery, 436
- Medial geniculate nucleus (MGN), 468
- Medial hypertrophy, 643
- Medial lemniscus, 484
- Medial longitudinal fasciculus, 513
- Medial medullary syndrome, 484
- Medial meniscal tear, 425
- Medial pterygoid muscle, 587
- Medial rectus muscle, 510
- Medial umbilical ligament, 270, 354
- Median, 251
- Median claw, 429
- Median nerve
  - carpal tunnel syndrome, 426
  - injury to, 427
- Median umbilical ligament, 354, 550
- Mediastinal lymph nodes, 93
- Mediastinitis, 133
- Medical abortion
  - ethical situations, 256
  - methotrexate for, 417
- Medical errors, **262**
- Medical power of attorney, 255
- Medicare/Medicaid, 260
- Medication errors, 262
- Medium-chain acyl-CoA dehydrogenase deficiency, 85
- Medroxyprogesterone, 622
- Medulla
  - lymph nodes, 92
  - thymus, 97
- Medulla (brain)
  - brain stem, 460
  - cranial nerves and nuclei, 474, 475
  - pyramids of, 474
  - spinal tracts and, 479
  - strokes in, 484–485
- Medullary carcinomas, 616
- Medullary cords (lymph nodes), 92
- Medullary cystic disease, 573
- Medullary pyramids (renal), 550
- Medullary thyroid carcinomas, 330, 339
  - oncogenes and, 218
- Medulloblastoma, 664, 498
- Mefloquine, 153
- Megacolon
  - Chagas disease, 154
  - in Hirschsprung disease, 367
- Megakaryocytes in essential thrombocytemia, 411
- Megaloblastic anemia, 396, 398
  - cytarabine, 417
  - *Diphyllobothrium latum*, 156
  - as drug reaction, 241
  - epilepsy drugs, 514
  - macro-ovalocytes in, 394
  - orotic aciduria, 398
  - trimethroprim, 190
  - tropical sprue as cause, 364
  - Vitamin B_9 deficiency, 64
  - vitamin B_{12} deficiency, 65
- Megestrol, 622
- Meglitinides, 341
- Meigs syndrome, 610
- Meissner corpuscles, 464
- Melanocytes
  - embryologic derivatives, 581
  - tumor nomenclature in, 216
  - in vitiligo, 448
- Melanocyte-stimulating hormone
  - secretion of, 313
  - signaling pathways of, 322
- Melanocytic nevus, 449
- Melanomas
  - nomenclature for, 216
  - oncogenes and, 218
  - of skin, 454
  - sunburn and, 453
  - tumor suppressor genes and, 218
- Melarsoprol, 152, 196
- Melasma, 448
- MELAS syndrome, 55
- Melatonin
  - circadian rhythms and, 467
  - derivation, 79
- Melena
  - Meckel diverticulum, 585
  - Meckel diverticulum as cause, 367
  - polyarteritis nodosa, 302
- Meloxicam, 456
- Memantine, 518
- Membrane attack complex (MAC), 100
  - complement and, 103
  - in type II hypersensitivity, 108
- Membranoproliferative glomerulonephritis (MPGN), 565
  - DPGN and, 564
  - hepatitis B and C, 169
- Membranous glomerular disorders, 563
  - hepatitis B and C, 169
- Membranous interventricular septum, 269
- Membranous nephropathy, 566, 660
- Membranous ossification, 434
- Membranous ventricular septum, 269
- Memory loss
  - anti-NMDA receptor encephalitis, 217
  - Wernicke-Korsakoff syndrome, 62, 481, 541
- *MEN1* gene, 218
- Ménétrier disease, **362**
- Ménière disease
  - vertigo with, 503
- Menin, 218
- Meninges, 465
- Meningiomas, 496
  - lab/findings, 660
  - Psammoma bodies in, 220
- Meningitis
  - ceftriaxone, 185
  - chloramphenicol, 188
  - coccidioidomycosis, 147
  - common causes, 176
  - *Cryptococcus neoformans*, 149
  - CSF findings in, 176
  - fluconazole, 195
  - flucytosine, 195
  - *Haemophilus influenzae*, 138
  - headaches with, 488
  - HIV-positive adults, 173
  - *Listeria monocytogenes*, 135
  - meningococci, 138
  - mumps as cause, 166
  - in neonates, 178
  - rifamycin prophylaxis, 192
  - *Streptococcus pneumoniae*, 132
  - *Streptococcus agalactiae*, 133
  - tuberculosis, 136
  - unvaccinated children, 182
- Meningocele, 461
- Meningococcal prophylaxis, 194
- Meningococcal vaccine, 124
- Meningococcemia
  - endotoxins, 127
  - meningococci, 138
- Meningococci, 138
- Meningoencephalitis
  - HSV-2, 178
  - *Naegleria fowleri*, 152
  - West Nile virus, 163
- Meningomyelocele, 461
- Meniscal tear, 424, 425
- Menkes disease, 46, **47**
- Menometrorrhagia, 597
- Menopause, **600**
  - fibroid tumors in, 612
  - hormone replacement therapy, 621
- Menorrhagia, 597
  - adenomyosis, 612
  - anemia with, 396
- Menstrual cycle, **597**
  - estrogens for, 621
- Meperidine, 520
- Mepivacaine, 519
- Mercury poisoning, 239
- Merkel discs, 464
- Merlin protein, 218
- Meropenem, 183, 186
- MERS (Middle East respiratory syndrome), 163
- Mesalamine, 365, 664
- Mesangial cells, 550
  - filtration, 553
  - juxtaglomerular apparatus, 558
- Mesencephalon, 460
- Mesenchymal tumors
  - nomenclature of, 216
  - vimentin stain for, 44
- Mesenteric arteries, 549
- Mesenteric ischemia, 369
  - presentation, 655
- Mesenteric veins, 350
- Mesocortical pathway, 468
- Mesoderm, 460
  - branchial arches derivation, 586
  - derivatives of, 581

Mesolimbic pathway, 468
Mesonephric duct, 589
Mesonephros, 548
Mesosalpinx, 592
Mesotheliomas, **641**
  carcinogens causing, 219
  Psammoma bodies in, 220
Mesovarium, 592
Mestranol, 621
Metabolic acidosis, 561
  adrenal insufficiency, 324
  Fanconi syndrome, 556
  neonatal respiratory distress syndrome, 627
  renal failure, 571
  symptoms of, 561
Metabolic alkalosis, 561
  acetazolamide for, 575
  causes of, 561
  Gitelman syndrome, 556
  hyperaldosteronism, 324
  hypertrophic pyloric stenosis as cause, 345
  loop diuretics, 575
  syndrome of apparent mineralocorticoid excess, 556
  thiazides, 576
Metabolic fuel use, **87**
Metabolic syndrome
  atypical antipsychotics, 543
  non-alcoholic fatty liver disease and, 374
Metabolism, **68–90**
  amino acid derivatives, 79
  amino acids, 77
  apolipoproteins, 89
  catecholamine synthesis/tyrosine catabolism, 79
  disorders of, 76, 77, 80–81, 83, 84–85, 90
  of drugs, **226**
  ethanol, **68**
  fatty acid, 85
  fuel use, 87
  gluconeogenesis, 74
  glycogen and, 82
  lipoprotein functions, 89
  pathway summary, 70
  pyruvate, 73
  rate-determining enzymes, 69
  sites of, 68
  TCA cycle, 73
  urea cycle, 78
Metabolites, 544
Metacarpophalangeal (MCP) joints, 429
Metachromatic leukodystrophy, 84, 494
Metalloproteinases, 211
Metal storage diseases, 210
Metanephric mesenchyme, 548
Metanephrines
  pheochromocytoma, 326
  tyrosine catabolism, 79
Metanephros, 548
Metaphase, 42
Metaphyseal tumors, 438
Metaplasia, 214
  benign breast disease, 615
  cervical, 592
  esophagus, 361
  gastric, 362
Metastases, **221**
  of liver cancer, 375
  of lung cancer, 647
  neoplastic progression in, 215
  ovarian, 664
Metastatic calcification, 208
Metastatic melanomas
  recombinant cytokines for, 117
  vemurafenib for, 421
Metencephalon, 460
Metformin, 340
  diarrhea caused by, 240
Methacholine, 232
Methacholine challenge, 638, **649**
Methadone, 520
  heroin addiction, 541
  intoxication and withdrawal, 540
  for opioid withdrawal, 540
Methamphetamine, 542
Methanol toxicity, 239
Methemoglobin, 632
  toxicity treatment, 239
Methemoglobinemia, 632
  local anesthetics and, 519
Methicillin, 240
Methimazole, 321, 341. *See also* Thionamides
  agranulocytosis, 241
  aplastic anemia, 241
  teratogenicity, 582
Methionine, 190
  classification of, 77
  start codons, 37
  tRNA charging, 40
Methotrexate, 417
  in cell cycle, 416
  folate deficiency, 398
  hydatidiform moles, 605
  megaloblastic anemia, 241
  polymyositis/dematomyositis, 445
  pulmonary fibrosis, 242
  pyrimidine synthesis and, 33
  rheumatoid arthritis, 439
  targets of, 416
  teratogenicity, 582
  toxicities of, 422
  toxicity, 639
  vitamin B_9 deficiency, 64
  as weak acid, 226
Methoxyflurane, 519
Methylation, 41
Methylcellulose, 383
Methyldopa
  Coombs-positive hemolytic anemia, 241
  hypertension in pregnancy, 304
Methylene blue, 239, 632
Methylmalonic acid
  vitamin B_9 deficiency, 64
  vitamin B_{12} deficiency, 65
Methylmalonyl-CoA mutase, 65
Methylmercury teratogenicity, 582
Methylphenidate
  for ADHD, 527, 542, 661
  CNS stimulant, 542
Methylprednisone, 455
Methyltestosterone, **623**
Methylxanthines, **649**
Metoclopramide, **383**
  Parkinson-like syndrome, 242
  tardive dyskinesia, 242
Metolazone, 576
Metoprolol, 237, 309
Metronidazole, **191**
  bacterial vaginosis, 144
  clindamycin vs, 188
  Clostridium difficile, 134
  for Crohn disease, 365
  disulfiram-like reaction, 242
  Giardia lamblia, 151
  Helicobacter pylori, 142
  mechanism (diagram), 183
  Trichomonas vaginalis, 664
  vaginal infections, 177
  vaginitis, 154
Metrorrhagia, 597
Metyrapone, 324
Metyrosine, 231
Mevalonate synthesis, 306
Mexiletine, 308
  arrhythmia, 661
Meyer loop, 511
MHC I and II, **96**
  cell surface proteins, 106
  dendritic cells and, 388
Micafungin, 194, 196
Michaelis-Menten kinetics, 224
Miconazole, 194, 195
Microalbuminuria, 336
Microangiopathic anemia, 401
  in anemia taxonomy, 396
Microangiopathic hemolytic anemia
  hypertensive emergency and, 290
  intravascular hemolysis in, 399
Microarrays, **50**
Microbiology, **120–200**
  antimicrobials, 183–200
  bacteriology, 120–130
  clinical bacteriology, 130–146
  mycology, 147–150
  parasitology, 151–157
  systems, 174–182
  virology, 158–173
Microcephaly
  cri-du-chat syndrome, 60
  fetal alcohol syndrome, 583
  maternal phenylketonuria, 80
  maternal X-ray exposure, 582
  Patau syndrome, 59
Microcytic anemia, **396**
  Ancylostoma, 157
  key associations, 667
Microcytosis, 212
Microfilaments (cytoskeleton), 44
Microglia, 460, **463**
Micrognathia
  Edwards syndrome, 59
  Pierre Robin sequence, 587
Microhematuria, 400
Micromelia, 582
Microphthalmia, 59
MicroRNAs, **39**
Microscopic polyangiitis, **302**
  labs/findings, 657
  RPGN and, 564
Microsporum, 148
Microtubule inhibitors, **419**
  in cell cycle, 416
Microtubules, 44
Midazolam, 515, 519
Midbrain
  development, 460
  lesions in, 481
Middle cerebellar peduncle, 474
Middle cerebral artery (MCA)
  in circle of Willis, 473
  cortical distribution, 472
  saccular aneurysms, 486
  stroke effects, 484
Middle meningeal artery
  epidural hematoma and, 483
Middle rectal vein, 350
Midgut
  blood supply/innervation of, 348
  development of, 344
Midodrine, 234
Midshaft of humerus, 432
Mifepristone, 622
Miglitol, 341
Migraine headaches, 488
  butorphanol for, 521
  hormonal contraception contraindication, 622
  TCAs as, prophylaxis, 545
  triptans for, 516
Migrating motor complexes (MMC), 356
Migratory polyarthritis, 300
Milestones (developmental), 258
Miliary tuberculosis, 136
Milnacipran, 545
Milrinone, 305
Mineralocorticoids
  adrenal insufficiency, 324
  adrenal steroids and, 318
Mineral oil, 61
Minimal alveolar concentration, 518
Minimal change disease, 566
Minocycline, 183, 188
Minors, consent for, 254
Minoxidil, **623**
Minute ventilation, 630
Miosis
  cholinesterase inhibitor poisoning, 232
  Horner syndrome, 509, 655
  opioids, 520
  Pancoast tumor, 646
  pupillary control, 509
  sympatholytic drugs, 235
Mirtazapine, 236, 546
  anorexia nervosa, 661
  major depressive disorder, 531
  mechanism of, 544
Mismatch repair, **37**

Misoprostol, **382**
  diarrhea, 240
Missense mutations, **36**
Mites/louse treatment, **196**
Mitiglinide, 341
Mitochondria
  high altitude and, 635
  metabolism in, 68
  muscle fibers, 433
Mitochondrial encephalopathy, 55
Mitochondrial inheritance, 55
Mitochondrial myopathies, 55
Mitosis, 42
  griseofulvin, 196
Mitral regurgitation
  in MI, 294
  murmurs caused by, 278, 279
  S3 heart sound, 668
  tuberous sclerosis, 495
Mitral stenosis
  left heart disease, 643
  murmurs caused by, 278, 279
Mitral valve
  in cardiac cycle, 276
  regurgitation in, 300
Mitral valve prolapse, 279
  fragile X syndrome, 58
  renal cyst disorders and, 573
Mittelschmerz, 596
Mivacurium, 520
Mixed cellularity lymphoma, 407
Mixed connective tissue disease, **443**
  anti-U1 RNP antibodies and, 39
  Raynaud phenomenon, 445
Mixed transcortical aphasia, 486
MMR vaccine, 158, 166
Mobitz AV blocks, 284
Modafinil, 538
Mode, 251
Molecular biochemistry, **32–41**
Molecular motor proteins, 44
Molluscum contagiosum, 160, 451
Mönckeberg sclerosis, 291
"Monday disease," 305
Monobactams, **186**
  mechanism (diagram), 183
  Pseudomonas aeruginosa, 139
Monoclonal gammopathy of undetermined significance (MGUS), 409
Monocytes, 386, **387**
  innate immunity and, 95
  morulae in, 145
Mononucleosis
  anemia and, 401
Monospot test, 161
Montelukast, 649
  arachidonic acid pathway, 455
Mood disorders, **530**
  readmissions with, 261
Moon facies, 323
Moraxella spp
  Gram-negative algorithm, 137
  taxonomy, 121
Moraxella catarrhalis
  rhinosinusitis, 636
Moro reflex, 258, 480
Morphine, 520
  for acute coronary syndromes, 296
  buprenorphine and, 228
  intoxication and withdrawal, 540
Morphogenesis of heart, 268–269
Morulae, 145
Mosaicism, **53**
Mosquitoes (disease vectors)
  lymphatic filariasis, 155
  malaria, 153
  Zika virus, 167
Motilin, 356
Motion sickness, 233
Motor cortex, 484
Motor neuron signs, **499**
Movement disorders, **489**
Moxifloxacin, 191
M phase, 42
MPO-ANCA, 111
M protein
  in multiple myeloma, 409
  rheumatic fever and, 132
  as virulence factor, 125
mRNA
  aminoglycosides, 187
  hepatitis viruses, 168
  pre-mRNA splicing, **39**
  processing, 38
  protease inhibitors, 199
  stop codons, **37**
  viral genome, 159
MRSA (methicillin-resistant *Staphylococcus aureus*)
  cephalosporins, 185
  highly resistant, 194
  nosocomial infections, 131
  oxazolidinones, 189
  vancomycin, 186
MSH. *See* Melanocyte-stimulating hormone (MSH)
mTOR, 116
Mucicarmine stain, 122
Mucinous cystadenocarcinomas, 611
Mucinous cystadenomas, 610
Mucociliary escalator, 628
Mucoepidermoid carcinomas, 359
Mucoid polysaccharide capsule, 139
Mucopolysaccharides, 122
Mucopolysaccharidoses, 84
Mucor spp
  amphotericin B for, 195
  opportunistic infection, 149
  presentation, 652
Mucormycosis, 149
  diabetic ketoacidosis, 337
Mucosa, 347
Mucosal bleeding
  scurvy, 656
Mucositis
  bleomycin, 418
  methotrexate, 417
Mucus, 230
Mulberry molars, 143
Müllerian duct
  agenesis, 589
  anomalies of, **590**
  derivatives of, 589
Müllerian inhibitory factor (MIF), 589
  Sertoli cell production, 594
Multicystic dysplastic kidney, **549**
Multifactorial pulmonary hypertension, 643
Multiorgan drug reactions, **242**
Multiple endocrine neoplasias (MEN syndromes), **339**
  Zollinger-Ellison syndrome, 338
Multiple myeloma, **409**
  ESR in, 212
  Fanconi syndrome, 556
  lab/diagnostic findings, 660
  osteoporosis, 435
  as plasma cell cancer, 389
Multiple sclerosis, **493**
  heart murmur with, 279
  HLA-DR2 and, 96
  IFN-β for, 200
  internuclear ophthalmoplegia, 513
  natalizumab for, 118
  oligodendroglia in, 464
  presentation, 655
  recombinant cytokines for, 117
  as type IV hypersensitivity, 109
Mumps, **166**
  acute pancreatitis caused by, 380
  paramyxovirus, 163, 165
  vaccine for, 107
Munchausen syndrome, 536
Munchausen syndrome by proxy, 536
Muscarinic acetylcholine (ACh) receptors, 229
Muscarinic antagonists, **233**, 649
  multiple sclerosis, 493
  neuromuscular blocking, 520
  Parkinson disease, 517
Muscle fibers, **433**
Muscle relaxants, 520
Muscles
  conduction to contraction, **433**
  metabolism in, 82
  ragged red fibers in, 55
Muscle spasms
  relaxants for, 520
Muscle tumors
  stain for, 44
Muscular dystrophies, **57**
  frameshift mutation, 36, 57
  presentation, 652, 656
  X-linked recessive disorder, 56
Muscularis externa, 347
Muscularis mucosa, 347
Muscular ventricular septum, 269
Musculocutaneous nerve, 427
Musculoskeletal drug reactions, **241**
Musculoskeletal system
  anatomy, 424–432
  pathology, 435–443
  pharmacology, 455–457
Mutases, 69
Mutations in DNA, **36**
Mutism, 536
Myalgias
  Ebola virus, 167
  fluoroquinolones, 191
  genital herpes, 180
  Jarisch-Herxheimer reaction, 143
  Lyme disease, 142
  meningitis, 182
  Trichinella spiralis, 157
  trichinosis, 155
Myasthenia gravis, **445**
  diagnosis of, 232
  neostigmine for, 232
  as paraneoplastic syndrome, 217
  pyridostigmine for, 232
  restrictive lung disease, 639
  type II hypersensitivity, 108
MYCL1 gene, 218
MYCN gene, 218
Mycobacterial cells, 192
Mycobacterium spp, **136**
  granulomatous diseases, 211
  intracellular organism, 124
  taxonomy, 121
Mycobacterium avium-intracellulare, **136**
  HIV-positive adults, 173
  prophylaxis with HIV, 194
  vertebral osteomyelitis, 176
Mycobacterium leprae
  animal transmission, 144
  diagnosis, 137
  rifamycins/dapsone, 192
Mycobacterium marinum, 136
Mycobacterium pneumoniae, 123
Mycobacterium scrofulaceum, 136
Mycobacterium tuberculosis, 136
  aerobic organism, 123
  culture requirements for, 123
  osteomyelitis, 176
  therapeutic agents, 192, 193
Mycolic acid
  isoniazid, 193
  synthesis of, 192
Mycology, **147–150**
Mycophenolate, 33
Mycophenolate mofetil, 116, 117
Mycoplasma spp
  atypical organisms, 175
  macrolides, 189
  pneumonia, 645
  pneumonia caused by, 175
Mycoplasma pneumoniae, **146**
  anemia and, 401
  erythema multiforme, 452
  tetracyclines, 188
Mycoses
  cutaneous, **148**
  granulomatous diseases, 211
  systemic, **147**
Mycosis fungoides, 408
Mydriasis
  α-agonists, 521
  G-protein-linked second receptor, 230
  muscarinic antagonists for, 233
  pupillary control, 509
  saccular aneurysm, 486
Myelencephalon, 460
Myelin, **464**
Myelodysplastic syndromes, **409**
  sideroblastic anemia, 397

Myelofibrosis, 411
  dacrocytes in, 394
Myeloperoxidase, 105
  in neutrophils, 386
Myeloproliferative disorders, **411**
  AML, 410
  basophilia, 387
  chronic, **411**
  hydroxyurea for, 419
Myelosuppression
  alkylating agents, 418
  antimetabolites, 417
  drugs causing, 422
  hydroxyurea, 419
  irinotecan/topotecan, 419
Myenteric nerve plexus, 347
Mylohyoid muscle, 587
Myocardial action potential, **280**
Myocardial depression, 519
Myocardial infarction (MI), 293
  β-blockers for, 237
  Class IB antiarrhythmics after, 308
  complications of, **295**
  diabetes mellitus, 336
  diagnosis of, **295**
  on ECG, 282
  evolution of, 294
  heart failure caused by, 298
  heparin for, 413
  homocystinuria, 80
  hypertensive emergency and, 290
  shock caused by, 299
  thrombolytics for, 415
Myocardial oxygen demand, 273
Myocarditis
  Corynebacterium diphtheriae, 135
  coxsackievirus, 163
  diptheria, 135
  picornaviruses, 163
  Toxocara canis, 155
Myoclonic seizures, 487
Myoclonus, 489
Myofibroblasts, 211
Myoglobin
  in muscle fibers, 433
  oxygen-hemoglobin dissociation curve, 632
Myoglobinuria
  acute tubular necrosis, 572
  McArdle disease, 83
Myometrium, 592
Myonecrosis, 134
Myopathy
  daptomycin, 191
  as drug reaction, 241
  interferons, 200
  lipid-lowering agents and, 306
Myophosphorylase, 83
Myopia, 504
  retinal detachment, 507
Myosin
  smooth muscle contraction, 434
  striated muscle contraction, 433
Myosin-light-chain kinase (MLCK), 434
Myotonic dystrophy
  cataracts and, 505
Myotonic type 1 muscular dystrophy, **57**
Myxedema
  hypothyroidism, 327
  thyroid hormones for, 342
Myxomas, 301
Myxomatous degeneration, 279

N

N-acetylcysteine, 648
  for acetaminophen toxicity, 239
  for cystic fibrosis, 56
N-acetylglucosaminyl-1-phosphotransferase, 43
NADH (nicotinamide adenine dinucleotide)
  electron transport chain, 74
  fructose metabolism, 76
  TCA cycle, 73
Nadolol, 237
NADPH (nicotinamide adenine dinucleotide phosphate)
  ethanol metabolism, 68
  HMP shunt and, 75
  respiratory burst and, 105
  universal electron acceptors, 71
Naegleria fowleri, **152**
Nafcillin
  characteristics of, 184
  mechanism (diagram), 183
Nails
  clubbing, 56
  glomus tumors under, 450
  splinter hemorrhages, 299
Naive T-cell activation, 99
Naked viral genome infectivity, **159**
Nalidixic acid, 183
Naloxone
  dextromethorphan overdose, 648
  heroin addiction, 541
  for opioid toxicity, 239
  opioid toxicity, 520, 540
Naltrexone
  alcoholism, 541, 661
  heroin addiction, 541
  opioid toxicity, 520, 540
Naproxen, 456
  acute gout drugs, 457
  arachidonic acid pathway, 455
Narcissistic personality disorder, 535
Narcolepsy, **538**
  amphetamines for, 234
  CNS stimulants for, 542
  hypnagogic hallucinations, 529
Nasal congestion, 648
Nasal decongestion
  ephedrine for, 234
Nasal polyps
  cystic fibrosis, 56
Nasal septum perforation, 302
Nasopharyngeal carcinomas
  EBV and, 161
  oncogenic microbes and, 219
Natalizumab, 118
  multiple sclerosis, 493
  progressive multifocal leukoencephalopathy, 494
Nateglinide, 341
National Board of Medical Examiners (NBME), 2, 10
Natriuresis, 558
Natural killer (NK) cells, **97**
  cell surface proteins, 106
  function of, 388
  innate immunity and, 95
Nausea
  adverse drug effects, 516
  Alzheimer disease drugs, 518
  anesthetics, 519
  cardiac glycosides, 307
  iron poisoning, 404
  loperamide as cause, 382
  MI as cause, 294
  migraine headaches, 488
  octreotide as cause, 382
  Parkinson disease drugs, 517
  polio presentation, 501
  ranolazine, 305
  renal failure, 571
  vitamin A toxicity, 62
  vitamin C toxicity, 65
NE. *See* Norepinephrine (NE)
Nebivolol, 237
Necator spp
  disease associations, 157
  infection routes, 154
Necator americanus, 155
Neck and head cancer, **636**
  cetuximab for, 420
Necrosis, **205**
  acute pancreatitis as cause, 380
  Arthus reaction, 109
  benign tumors, 216
  calcification, 208
  carbon tetrachloride, 219
  caseating, 211
  femoral head, 116, 436
  fibrinoid, 439
  glioblastoma multiforme, 496
  hepatic, 455
  ischemic brain disease, 482
  jaw, 456
  retinitis, 508
  saponification, 205
  scaphoid avascular, 426
  skin, 452
  transplant reaction, 115
  warfarin, 414
Necrotizing enterocolitis, 369
  low birth weight, 599
  neonatal respiratory distress syndrome and, 627
Necrotizing fasciitis, 132, 451
Necrotizing glomerulonephritis, 302
Negative predictive value (NPV), 247, 669
Negative reinforcement, 524
Negative skew distribution, 251
Negative-stranded viruses, 164
Neglect (child), **526**
Negri bodies, 167
Neisseria spp, **138**
  C5-C9 deficiencies, 103
  cephalosporins, 185
  fluoroquinolones, 191
  IgA protease, 125
  intracellular organism, 124
  taxonomy, 121
  transformation in, 126
Neisseria gonorrhoeae, 138
  antigenic variation, 106
  culture requirements, 123
  Gram-negative algorithm, 137
  osteomyelitis, 176
  pelvic inflammatory disease, 181
  septic arthritis, 441
  STI, 180
  UTIs with, 570
Neisseria meningitidis
  chloramphenicol, 188
  culture requirements, 123
  encapsulation, 124
  Gram-negative algorithm, 137
  immunodeficient patients, 114
  meningitis, 176
  penicillin G/V for, 183
  splenic dysfunction, 94
  Waterhouse-Friderichsen syndrome, 324
Nelson syndrome, **332**
Nematodes, **155**
  infection routes, 154
Neomycin
  aminoglycosides, 187
  for hepatic encephalopathy, 374
  mechanism (diagram), 183
Neonatal respiratory distress syndrome (NRDS), **627**
  restrictive lung disease, 639
Neonates
  ABO hemolytic disease of, **390**
  Apgar score, 599
  Candida albicans in, 149
  Chlamydia trachomatis in, 146
  coagulation cascade in, 392
  conjunctivitis, 138, 146
  deprivation effects, **526**
  esophageal atresia in, 344
  flora with C-section, 174
  galactosemia in, 76
  gastroenteritis, 164
  gray baby syndrome in, 188
  hemolytic anemia in, 400
  herpes in, 160
  HIV in, 171
  hyperthermia in, 233
  hypertrophic pyloric stenosis in, 345
  indirect inguinal hernia in, 355
  jaundice in, **376**
  kernicterus, 190, 201
  Listeria monocytogenes in, 135
  low birth weight, 599
  meningitis in, 135, 178
  necrotizing enterocolitis and, 369
  Nikolsky sign, 451
  obesity risk factors, 599
  pneumonia in, 146
  primitive reflexes in, 480

  Rh hemolytic disease of, **390**
  sickle cell anemia in, 400
  Streptococcus agalactiae in, 133
  vitamin deficiencies, 66
Neoplasia, **204–211**
  pathology of, 214–221
  progression of, **215**
Neostigmine, 232, 520
Nephritic-nephrotic syndrome, 563
Nephritic syndrome, 563, **564–565**, 566
Nephritis, 575
Nephrogenic diabetes insipidus, 334
Nephrolithiasis, 569
  calcium oxalate, 65
Nephron physiology, **555**
Nephropathy
  diabetes mellitus, 336
  hypertension and, 290
  membranous, 111, 660
  protease inhibitors, 199
  transplant rejection, 115
Nephrotic syndrome, 563, **566**
  amyloidosis and, 213
  charge barrier in, 551
  ESR in, 212
  fatty casts in, 562
  labs/findings, 660
  loop diuretics for, 575
  pleural effusion, 644
  presentation, 655
Nephrotoxicity
  aminoglycosides, 187
  amphotericin B, 195
  cidofovir, 198
  cisplatin/carboplatin, 419
  cladribine, 417
  as drug reaction, 242
  drugs causing, 422
  immunosuppressants, 116
  inhaled anesthetics, 519
  streptomycin, 193
  sulfonamides, 190
  vancomycin, 186
Nerve blockade in local anesthetics, 519
Nerve fibers, 465
Nerves
  lower extremity, **430**
  upper extremity, **427**
Nerve trunk, 465
Net filtration pressure, 553
Neural crest
  derivatives of, 581
Neural crest cells, 460, 464
  neuroblastomas in, 325
Neural development, **460**
Neural fold, 460
Neural plate, 460
Neural tube, 460
  fetal development, 580
Neural tube defects, **461**
  labs/findings, 657
  maternal diabetes, 582
  prevention, 64
  valproic acid, 514
  vitamin deficiency, 668
Neuraminidase, 165, 166
Neuroblastomas, **325**
  Homer-Wright rosettes, 658
  labs/findings, 668
  neurofilament stain for, 44
  oncogenes and, 218
  opsoclonus-myoclonus ataxia syndrome, 217
Neurocutaneous disorders, **495**
Neurocysticercosis, 156
Neuroectoderm, 460
  astrocytes derived from, 463
  derivatives of, 580
  pituitary gland, 313
  teratomas, 611
Neuroendocrine tumors, **325**
Neurofibromatosis, 495, 505
  chromosome association, 60
  inheritance, 56
  variable expressivity, 52
Neurofibromatosis type 1
  presentation, 652
  tumor suppressor genes and, 218
Neurofibromatosis type 2
  presentation, 652
  tumor suppressor genes and, 218
Neurofilaments, 44
Neurogenic ileus, 232
Neurohumoral transmission, 229
Neurohypophysis, 313
  hypothalamus and, 466
Neuroleptic drugs, 537
Neuroleptic malignant syndrome, 520
Neuroleptic malignant syndrome (NMS), 543
Neurologic drug reactions, 242
Neurology, 460–514
  anatomy/physiology, 463–485
  embryology, 460–462
  ophthalmology, 504–511
  pathology, 481–488
  pharmacology, 514–521
Neuromuscular blocking drugs, **520**
Neuromuscular junction diseases, **445**
Neuromuscular paraneoplastic syndromes, 217
Neuronal tumors, 44
Neurons, **463**
  local anesthetics, 519
  origins of, 460
  Parkinson disease, 517
Neuropathic pain, 485
Neuropathy
  amyloidosis and, 213
  diabetes mellitus, 336
Neurosyphilis, 143
  dementia, 529
Neurotoxicity
  cladribine, 417
  immunosuppressants, 116
  methylmercury exposure, 582
  methylxanthines, 649
  vincristine, 419
Neurotransmitters, **465**
Neurovascular pairing, **432**
Neutralization (antibody), 100
Neutropenia
  ganciclovir, 198
  interferons, 200
  rheumatoid arthritis, 439
Neutropenias, 402
  ticlopidine, 415
Neutrophil chemotaxis
  endotoxins and, 129
Neutrophils, **386**
  chemotaxis, 103
  CML, 410
  corticosteroid effect on, 402
  IL-8 and, 104
  inflammation and, 207
  innate immunity and, 95
  in leukocyte adhesion deficiency, 113
  megaloblastic anemia, 398
  in MI, 294
  necrosis and, 205
  nonmegaloblastic anemia, 398
  pseudo-Pelger-Huet anomaly, 409
  wound healing, 211
Nevi, 216
Nevirapine
  cytochrome P-450 and, **243**
  HIV therapy, 199
  mechanism (diagram), 197
Nevus flammeus
  presentation, 656
  Sturge-Weber syndrome, 495
NF1 gene, 495
  pheochromocytomas and, 326
NF1/*NF2* genes, 218
NF-κB, 116
N-formylmethionine (fMet), 37
Niacin
  cutaneous flushing, 239
  gout, 241
  hyperglycemia, 240
  myopathy caused by, 241
  tachyphylactic drug interaction, 225
Nicardipine, 304
Nicotinamides, 71
Nicotine intoxication and withdrawal, 540
Nicotinic acetylcholine receptors, 162, 229
Niemann-Pick disease, 84, 652
Nifedipine, 304, 608
Nifurtimox, 154, 196
Night sweats
  Pott disease, 652
Night terrors, 467, 515
Nigrostriatal pathway, 468
Nikolsky sign, 451
  pemphigus vulgaris, 452
Nimodipine, 304, 483
Nipple
  eczematous patches, 616
  intraductal papilloma, 615
  lactational mastitis, 615
  rash on, 655
Nissl bodies, 42
Nissl substance
  chromatolysis, 465
  neurons, 463
Nitazoxanide, 151
Nitrates, 305
Nitric oxide, 356
  derivation, 79
  free radical injury and, 210
Nitric oxide synthase, 434
Nitrites
  methemoglobin, 632
  urinary tract infections, 177
Nitroblue tetrazolium dye reduction test, 113
Nitrofurantoin
  hemolysis in G6PD deficiency, 241
  pulmonary fibrosis, 242
Nitroglycerin, 305
  acute coronary syndromes, 296
  angina, 293
Nitroprusside, 304
Nitrosamines
  as carcinogens, 219
  stomach cancer and, 362
Nitrosoureas, 418
Nitrous oxide, 519
Nizatidine, 381
N-*myc* oncogene, 325
Nocardia spp
  Actinomyces spp vs, 135
  aerobe, 123
  catalase-positive organism, 124
  Gram-positive algorithm, 130
  immunodeficient patients, 114
  necrosis and, 205
  sulfonamides for, 190
  taxonomy, 121
  urease-positive, 124
Nocturia, 619
Nocturnal enuresis, 317, 467
Nodes of Ranvier, 464
Nodular phlebitis, 302
Nodular sclerosing Hodgkin lymphoma, 668
Nodular sclerosis lymphoma, 407
Noise-induced hearing loss, 503
Nonadherent patients, 256
Non-alcoholic fatty liver disease, **374**
Nonbacterial thrombotic endocarditis, 217
Nonbenzodiazepine hypnotics, **515**
Noncaseating granulomas
  restrictive lung disease, 639
  sarcoidosis, 444
Noncommunicating hydrocephalus, 492
Noncompetitive agonists, 228
Noncompetitive inhibitors, 224
Nondisjunction (meiosis), **59**
Nondominant parietal cortex lesions, 481
Nonhemolytic anemia, **399**
Non-Hodgkin lymphoma, **407**, **408**
  associations, 668
  corticosteroids, 116
  Hashimoto thyroiditis and, 328
  hepatitis C, 169

Non-Hodgkin lymphoma *(continued)*
  HIV-positive adults, 173
  Hodgkin lymphoma vs, **407**
  oncogenes and, 218
  rituximab for, 118, 420
  vinca alkaloids for, 419
Nonhomologous end joining, **37**
Nonmaleficence (ethics), 253
Nonmegaloblastic macrocytic anemia, 398
Nonnormal distributions, 251
Nonreceptor tyrosine kinase, 322
Non-REM sleep stages, 467
Non-response bias, 250
Nonsense mutations, **36**
Nonsteroidal anti-inflammatory drugs (NSAIDs), **456**
  acute gout attack, 661
  acute interstitial nephritis, 572
  aplastic anemia, 241
  Beers criteria, 238
  calcium pyrophosphate deposition disease, 440
  endometriosis, 613
  gastric ulcers caused by, 363
  gastritis caused by, 362
  gout, 440, 457
  headaches, 488
  interstitial nephritis, 240, 242
  loop diuretics and, 575
  lupus, 443
  membranous nephropathy, 566
  osteoarthritis, 439
  prostaglandin synthesis, 559
  renal papillary necrosis, 572
  rheumatoid arthritis, 439
Non-ST-segment elevation MI
  diagnosis of, 295
  STEMI vs, 293
  treatment, 296
Noradrenergic drugs, 231
Norepinephrine (NE). *See also* Catecholamines
  adrenal medulla secretion, 312
  amphetamines and, 231
  bupropion effect on, 546
  changes with disease, 465
  circadian rhythm, 467
  direct sympathomimetic, 234
  isoproterenol vs, **235**
  male sexual response, 593
  MAO inhibitor effects, 546
  in nervous system, 229
  opioid effect on, 520
  phenoxybenzamine and, 228
  pheochromocytoma secretion, 326
  REM sleep and, 467
  tramadol effects, 521
  tyrosine catabolism, 79
  vitamin B_6 and, 63
Norethindrone, 622
Norfloxacin, 191
Normal distribution, 251
Normal pressure hydrocephalus, 492
Normal splitting, 277
Normetanephrine, 79
Normocytic anemia, 396, **399**
Norovirus
  medical improtance, 163
  watery diarrhea, 175
Northern blot, 49
Nortriptyline, 545
Nosocomial infections, **181**, 262
  Ebola, 167
  Klebsiella, 140
  pneumonias, 175
  Pseudomonas aeruginosa, 139
  UTIs as, 177
Notochord, 460
  postnatal derivative of, 270
Novobiocin
  Gram-positive antibiotic test, 130
  Staphylococcus epidermidis, 131
NPH insulin, 340. *See also* Insulin
NSE hormone, 325
Nuclear envelope, 43
Nucleic acids
  pathogen-associated molecular pattern (PAMP), 95
  synthesis of, 194
  in viruses, 158
Nucleosides, 33
Nucleotide excision repair, **37**
Nucleotides, **33**
  synthesis, 68
Nucleotide triphosphate, 48
Nucleus ambiguus, 477
Nucleus cuneatus, 479
Nucleus pulposus
  collagen in, 46
  fetal precursor, 270
Nucleus pulposus herniation, 478
Nucleus solitarius, 477
Null hypothesis, 251, 252
Number needed to harm (NNH), 248, 669
Number needed to treat (NNT), 248, 669
Nutmeg liver, 298, 375
Nutrition, **61–68**
Nyctalopia, 62
Nystagmus
  cerebellum, 469
  common lesions and, 481
  Friedreich ataxia, 501
  internuclear ophthalmoplegia, 513
  multiple sclerosis, 493, 655
  PCP as cause, 541
  stroke and, 484
  vertigo and, 503
Nystatin, **195**
  Candida albicans, 149, 661
  mechanism (diagram), 194

O

Obesity
  acanthosis nigricans, 453
  amphetamines for, 234
  anovulation with, 609
  breast cancer risks, 616
  cholelithiasis and, 379
  Cushing syndrome, 323
  DM type 2 and, 337
  empty sella syndrome and, 335
  endometrial cancer, 612
  esophageal cancer and, 361
  focal segmental glomerulosclerosis, 566
  hypertension risk factors, 290
  lateral femoral cutaneous nerve, 430
  leptin gene mutation, 317
  olanzapine, 543
  osteoarthritis/rheumatoid arthritis, 439
  PCOS and, 609
  Prader-Willi syndrome, 54
  renal cell carcinoma, 568
  sleep apnea, 642
  stress incontinence and, 569
Obesity hypoventilation syndrome, 642
Obligate intracellular organisms, 124
Oblique fissure, 629
Observational studies, **246–253**
  errors in, 250
Observer-expectancy bias, 250
Obsessive-compulsive disorder (OCD), **533**
  antipsychotic drugs for, 543
  atypical antipsychotics for, 543
  drug therapy for, 542
  SSRIs for, 545
  Tourette syndrome and, 527
  tricyclic antidepressants for, 545
  venlafaxine for, 545
Obsessive-compulsive personality disorder, 535
Obstructive jaundice, 380
Obstructive lung diseases, **638**
  flow volume loops in, 637
Obstructive shock, 299
Obstructive sleep apnea, 642
  pulse pressure in, 272
  pulsus paradoxus in, 300
Obturator nerve, 430
Occipital cortex, 485
Occipital lobe, 471
Occipital sinus, 473
Occult bleeding, 370
Octreotide, 356, **382**
  acromegaly, 333
  carcinoid syndrome, 338
  for carcinoid syndrome, 661
  GH excess, 317
  glucagonomas, 338
  hypothalamic/pituitary drugs, 342
Ocular albinism, 56
Ocular hyperemia, 521
Ocular motility, **510**
Ocular muscles, 510
Oculomotor nerve (CN III), **476**
  brain stem location, 474
  cavernous sinus, 512
  location in brain stem, 474
  ocular motility, 510
  palsy of, 483, 511
  pathway for, 476
  pupillary contraction, 509
Odds ratio, 669
Odds ratio (OR), 246, 248
Odontoblasts, 581
Ofloxacin, 191
Okazaki fragments, 35
Olanzapine, 543
Olfactory bulb, 474
Olfactory hallucinations, 529
Olfactory nerve (CN I), **476**
  brain stem location, 474
  pathway for, 476
Olfactory tract, 474
Oligoclonal bands, 493
Oligodendrocytes, 464, 494
Oligodendroglia, 460
Oligodendrogliomas, 496
Oligohydramnios, 607
  Potter sequence, 548
Oligomenorrhea, 597, 609
Oligomycin, 74
Oligospermia, 382
Oliguria, 564
Omalizumab, 118, 649
Omental foramen, 346
Omeprazole, 381
Omphalocele, 344
Omphalomesenteric cysts, 367
Onchocerca volvulus, 154, 155
Oncogenes, **218**
Oncogenic microbes, **219**
Ondansetron, **383**
  torsades de pointes, 239
$1,25\text{-(OH)}_2D_3$
  kidney endocrine function, 559
  renal osteodystrophy, 571
Onychomycosis
  terbinafine, 195
  tinea unguium, 148
Oogenesis, **596**
Oophorectomy, 592
Open-angle glaucoma, 506
  carbachol for, 232
  epinephrine for, 234
  pilocarpine for, 232
Operant conditioning, **524**
Ophthalmology, 504–511
Ophthalmoplegia
  cavernous sinus syndrome, 512
  common lesions with, 481
  internuclear, 513
  multiple sclerosis, 493
  Wernicke-Korsakoff syndrome, 62, 541
Opioids, **520**
  Beers criteria, 238
  intoxication and withdrawal, 540
  intravenous anesthetics, 519
  pentazocine and, 521
  sleep apnea, 642
  toxicity treatment, 239
Opponens digiti minimi muscle, 429
Opponens pollicis muscle, 429
Opportunistic fungal infections, **149–150**
Oppositional defiant disorder, 527
Oprelvekin, 117

Opsoclonus-myoclonus syndrome, 217, 325
Opsonins, 103
Opsonization, 94, 100, 103
Optic atrophy
  Krabbe disease, 494
Optic canal, 476
Optic chiasm, 474
  circle of Willis, 473
  pupillary reaction, 509
Optic disc, 504
  papilledema in, 508
Optic gliomas
  neurofibromatosis, 495, 652
Optic nerve (CN II), **476**
  anatomy, 504
  embryologic derivation, 581
  Marcus Gunn pupils, 509
  optic tract, 474
  pathway, 476
Optic neuritis, 493
Optic neuropathy, 193
Optochin
  Gram-positive antibiotic test, 130
  viridans streptococci, 132
Oral advance directives, **255**
Oral contraceptives (OCPs)
  cytochrome P-450 and, 243
  endometriosis, 613
  hepatic adenomas and, 375
  melasma and, 448
  ovarian neoplasms, 610
  PCOS, 609
  prolactin effects on, 316
  reproductive hormones, 620
  SHBG effects on, 322
Oral glucose tolerance test, 336
Oral hairy leukoplakia, 173
Oral rehydration therapy, 141
Oral thrush, 173
Orange body fluids, 192
Orchiectomy, 617
Orchiopexy, 617
Orchitis, 166
Orexigenic effect, 317
Orexin, 538
Organ failure, in acute pancreatitis, 380
Organogenesis
  errors in, **581**
  fetal development, 580
  teratogens, **582**
Organomegaly, 569
Organophosphates
  poisoning by, 232
  toxicity treatment, 239
Organ transplants
  azathioprine for, 417
  cytomegalovirus, 182
  hairy leukoplakia and, 451
  kidneys, 550
  WBC casts, 562
Organum vasculosum of the lamina terminalis (OVLT), 466
Orientation, **528**
Origin of replication, 35
Orlistat, **383**
  diarrhea, 240
Ornithine
  cystinuria, 81
  kidney stones and, 567
  urea cycle, 78
Ornithine transcarbamylase, 70
Ornithine transcarbamylase deficiency, **79**
  inheritance, 56
Orotic acid, 79
Orotic aciduria, 398
  in anemia taxonomy, 396
"Orphan Annie eyes" nuclei, 330, 658
Orthomyxoviruses
  characteristics of, 163, 164
  influenza viruses, 165
  segmented, 164
Orthopnea, 298
Orthostatic hypotension
  adrenal insufficiency, 324
  α-blockers, 236
  phenoxybenzamine, 236
  SGLT2, 341
Oseltamivir, 197
Osler nodes, 655
  bacterial endocarditis, 299
Osmotic demyelination syndrome, **492**
  SIADH and, 334
Osmotic diarrhea, 364
Osmotic diuresis
  hyperosmolar hyperglycemic state, 338
  insulin deficiency/insensitivity, 336
Osmotic laxatives, 383
Ossicles, 503
Osteitis fibrosa cystica, 332, 434, 437, 657
Osteoarthritis, **439**
  celecoxib for, 456
  presentation, 656
Osteoblasts, 434
  bone formation, 434
  cortisol effect on, 319
  Paget disease of bone, 436
  teriparatide effect on, 457
Osteochondromas, 438
Osteoclasts, 434
  bisphosphonate effects, 456
  bone formation, 434
  Paget disease of bone, 436
Osteodystrophy, 382
Osteogenesis imperfecta, **47**
  bisphosphonates, 456
  collagen and, 46
  presentation, 652
Osteogenic sarcomas, 436
Osteomalacia
  hypophosphatemia, 560
  vitamin D deficiency, 66, 319
Osteomalacia/rickets, **436**
  lab values in, 437
Osteomas
  nomenclature for, 216
Osteomyelitis, **176**
  diagnostic findings, 660
  Pseudomonas aeruginosa, 139
  sickle cell anemia, 400
  Staphylococcus aureus, 131
Osteonecrosis, **436**
  bisphosphonates causing, 456
Osteopenia, 436
Osteopetrosis, **435**, 437
Osteophytes, 439
Osteoporosis, **435**
  bisphosphonates, 456
  corticosteroids, 116
  Cushing syndrome, 323
  denosumab, 118
  as drug reaction, 241
  estrogen, 434
  Gaucher disease, 84
  heparin, 413
  homocystinuria, 80
  hormone replacement therapy, 621
  lab values in, 437
  menopause, 600
  pituitary prolactinomas, 315
  raloxifene for, 621, 421
  teriparatide for, 457
  thiazides for, 576
  vertebral compression fractures, 668
Osteosarcomas, 438
  nomenclature for, 216
  tumor suppressor genes and, 218
Otitis externa, 139
Otitis media
  brain abscesses caused by, 176
  Haemophilus influenzae, 125, 138
  Langerhans cell histiocytosis, 412
  Streptococcus pneumoniae, 132
  Wegener granulomatosis as cause, 302
Otology, **503**
Ototoxicity
  aminoglycosides, 187, 201
  aminoglycoside teratogenicity, 582
  cisplatin/carboplatin, 419
  as drug reaction, 242
  ethacrynic acid, 575
  loop diuretics, 575
  vancomycin, 186
Ouabain, 45
Outcome (quality measurement), 261
Outer membrane, 120
Outflow tract formation, 269
Ovarian artery, 592
Ovarian cancer
  breastfeeding and, 599
  cisplatin/carboplatin for, 419
  epidemiology of, 608
  hypercalcemia and, 217
  irinotecan/topotecan for, 419
  Lynch syndrome and, 371
  oncogenes and, 218
  paclitaxel for, 419
  Psammoma bodies in, 220
  tumor suppressor genes and, 218
Ovarian cycle, 597
Ovarian cysts, **610**
Ovarian dysgenesis, 603
Ovarian ligament, 592
Ovarian teratomas, 217
Ovarian tumors, **610–611**
Ovaries
  anatomy of, 592
  descent of, **591**
  embryologic derivation, 581
  epithelial histology, 592
  estrogen production, 595
  lymphatic drainage, 591
  premature failure, 609
Overactive bladder, 569
Overflow incontinence, 569
Oviducts, 589
Ovotesticular disorder, 603
Ovulation, **596**
  anovulation causes, 609
  progesterone and, 595
  prolactin effect on, 316
Owl eye inclusions, 658
Oxacillin
  characteristics of, 184
  mechanism (diagram), 183
Oxazepam, 515
Oxazolidinones, **189**
Oxidative phosphorylation, **74**
  metabolic site, 68
  poisons, 74
Oxybutynin, 233
Oxygen
  in blood, 633
  for carbon monoxide poisoning, 239
  carboxyhemoglobin, 632
  cluster headaches, 488
  deprivation, **634**
  exercise and, 635
  hemoglobin, 631
Oxygen-hemoglobin dissociation curve, **632**
Oxygen toxicity, 210
Oxytocin
  hypothalamic/pituitary drugs, 342
  hypothalamus production, 466
  lactation and, 599
  pituitary gland and, 313
  signaling pathways for, 322

P

P-450, 193
Pacemaker action potential, **281**
Pacinian corpuscles, 464
Paclitaxel, 419
  in cell cycle, 416
  microtubules and, 44
  targets of, 416
Paget disease of bone, **436**
  bisphosphonates, 456
  lab values in, 437
  osteosarcomas and, 438
  presentation, 652
  woven bone in, 434
Paget disease of breast, 614, 616
  presentation, 655
Pain receptors, 464

Palatine shelves, 588
Pale infarct vs red infarct, 207
Paliperidone, 543
Palivizumab, 118
  pneumonia prophylaxis, 165
  for RSV, 200
Pallor in aplastic anemia, 399
Palmar crease, 656
Palmar erythema, 372
Palmar interossei, muscle, 429
Palmar reflex, 480
Panacinar emphysema, 638
p-ANCA, 111
  sclerosing cholangitis and, 378
Pancoast tumor, **646**
  Horner syndrome and, 509
  labs/findings, 657
  lung cancer, 647
  superior vena cava syndrome, 646
  thoracic outlet syndrome, 428
Pancreas
  biliary structures and, 353
  blood supply and innervation of, 348
  embryology, 345
Pancreas divisum, 345
Pancreatic buds, 345
Pancreatic cancer, **380**
  5-fluorouracil for, 417
  adenocarcinomas, **380**
  biliary cirrhosis and, 378
  carcinogens causing, 219
  hyperbilirubinemia caused by, 376
  metastases of, 221
  nonbacterial thrombotic endocarditis and, 217
  oncogenes and, 218
  presentation, 655
  Trousseau's syndrome and, 217
  tumor suppressor genes and, 218
Pancreatic cells, **313**. *See also* α cells; β cells; Δ cells
Pancreatic ducts, 345, 353
Pancreatic insufficiency, 364
  chronic pancreatitis as cause, 380
Pancreatic lipase, 88
Pancreatic secretions, **358**
Pancreatitis, **380**
  acute respiratory distress syndrome as cause, 642
  alcoholism, 541
  corticosteroids and, 240
  as drug reaction, 240
  GLP-1 analogs and, 341
  hyperchylomicronemia, 90
  hyperparathyroidism as cause, 332
  hypertriglyceridemia, 90
  mumps, 166
  necrosis and, 205
  NRTIs, 199
  pancreas divisum as cause, 345
  pancreatic insufficiency caused by, 364
  valproic acid, 514
Pancuronium, 520
Pancytopenia, 399
  Chédiak-Higashi syndrome, 113
  cytarabine, 417
  Gaucher disease, 84
  leishmaniasis, 154
  osteopetrosis and, 435
  paroxysmal nocturnal hemoglobinuria, 400
Pandemics, 165
Panic disorder, 532, **533**
  drug therapy for, 542
  SSRIs for, 545
  venlafaxine for, 545
Pansystolic murmur, 278
P antigen, 165
Pantoprazole, 381
Papillary carcinomas, 216
Papillary muscle
  blood supply to, 296
  rupture, 294, 296
Papillary thyroid carcinomas, 330
  carcinogens causing, 219
  labs/findings, 660
  Psammoma bodies in, 220
Papilledema, 491, **508**
  hypertensive emergency and, 290
Papillomas, 216
Papillomaviruses
  characteristics of, 160
  DNA viruses, 159
  genome, 158
PAPP-A
  autosomal trisomies, 59
Pap smear, 609
Papules, 447
Para-aminohippuric acid (PAH), 552
Para-aortic lymph nodes, 93, 591
Paracoccidioidomycosis, **147**
Paracortex (lymph node), 92
Paracrine, 559
Paradoxical splitting, 277
Paraesophageal hernias, 355
Parainfluenza
  croup, 166
  paramyxovirus, 163, 165
Parakeratosis, 448
Paralysis
  conversion disorder, 536
  Guillain-Barré syndrome, 493
  poliovirus, 182
  rabies, 167
  unvaccinated children, 182
Paralytic ileus, 419
Paramedian pontine reticular formation lesions, 481
Paramesonephric duct, 589
Paramyxoviruses, **165**
  characteristics of, 163, 164
  croup, 166
  measles, 166
  mumps, 166
Paraneoplastic cerebellar degeneration, 217
Paraneoplastic encephalomyelitis, 217
Paraneoplastic syndromes, **217**
  lung cancer, 647
  renal cell carcinoma and, 568
  renal tumors, 668
Paranoia
  amphetamines, 540
  LSD as cause, 541
Paranoid personality disorder, 535
Parasites
  eosinophilia with, 387
Parasitology, **151–157**
Parasympathetic nervous system, 229
  male erection, 593
Parasympathetic receptors, 230
Parathyroid adenomas
  hyperparathyroidism caused by, 332
  MEN 1/MEN 2A syndromes, 339
Parathyroid disease diagnosis, **331**
Parathyroid hormone (PTH), **320**
  bone disorders, 437
  bone formation, 434
  calcitonin and, 321
  in hyperparathyroidism, 332
  kidney effects, 559
  nephron physiology, 555
  osteomalacia/rickets, 436
  Paget disease of bone, 436
  pseudohypoparathyroidism and, 331
  signaling pathways of, 322
  thymic aplasia, 112
  vitamin D and, 319, 320
Parathyroid tumors
  presentation, 655, 656
Paraumbilical vein, 350
Parental consent, 254
Paresthesias
  panic disorder, 533
  vitamin B_{12} deficiency, 65
Parietal cell
  autoantibody, 111
Parietal lobe, 471
Parietal peritoneum, 354
Parinaud syndrome, 475, 481, 498
Parkinson disease, 490
  basal ganglia lesions, 481
  benztropine for, 233
  dopaminergic pathways, 468
  drug therapy for, **517**
  Lewy bodies, 490
  neurotransmitters for, 465
  nigrostriatal pathway and, 468
  presentation, 655
  proteasome and, 43
  resting tremor in, 489
Parkinsonism
  Wilson disease as cause, 378
Parkinson-like syndrome, 242
Parotid gland
  embryologic derivation, 581
  enlargement of, 441
  tumors in, 359
Parotitis
  bulimia nervosa, 537
  mumps, 166
Paroxetine, 545
Paroxysmal nocturnal dyspnea, 298
Paroxysmal nocturnal hemoglobinuria, 400
  in anemia taxonomy, 396
  CD55 deficiency, 103
  eculizumab for, 118
  flow cytometry diagnosis, 50
  intravascular hemolysis in, 399
  presentation, 655
Pars planitis, 506
Partial agonists, 228
Partial pressure, 633
Partial seizures, 487
Parvovirus
  characteristics of, 160
  DNA viruses, 159
  genome of, 158
  naked viruses, 159
Parvovirus B19
  aplastic anemia, 399
  hereditary spherocytosis, 400
  hydrops fetalis, 178
  rash, 179
  receptors, 165
Passive aggression, 525
Passive immunity, **107**
Pasteurella spp
  Gram-negative algorithm, 137
  taxonomy, 121
Pasteurella multocida
  osteomyelitis, 176
  transmission, 144, 182
Patau syndrome, **59**
  cataracts, 505
  chromosome association, 60
  hCG in, 598
  holoprosencephaly, 461
  horseshoe kidney and, 549
Patches, 447
Patellar reflex
  lumbosacral radiculopathy, 432
Patent ductus arteriosus (PDA)
  congenital rubella, 290
  fetal alcohol syndrome, 290
  heart murmur with, 279
  indomethacin for, 456
  mechanism and treatment, 289
  misoprostol for, 382
  neonatal respiratory distress syndrome and, 627
Patent foramen ovale
  atrial septal defect vs, 289
  septal fusion failure, 268
Patent urachus, 585
Pathogen-associated molecular patterns (PAMPs), 95
Pathogenic *Escherichia coli* (EPEC), 140
Pathologic grief, **532**
Pathology, **203–221**
  cardiovascular, 288–302
  endocrine, 323–339
  gastrointestinal, 359–380
  hematologic/oncologic, 394–414
  inflammation, 204–213
  musculoskeletal/skin/connective tissue, 435–443
  neoplasia, 214–221
  neurological, 481–488
  psychiatric, 526–540
  renal, 562–573
  reproductive, 603–617
  respiratory, 636–646
  USMLE Step 1 preparation for, 265
Patient payment models, **260**

- Pavlovian conditioning (classical conditioning), 524
- PCO$_2$, 630
- PCP (phencyclidine)
  - intoxication and withdrawal, 541
- PCSK9 inhibitors, 306
- PDE-3, 305
- PDE-5 inhibitors, 619, **623**
  - benign prostatic hyperplasia, 661
  - naming convention for, 244
- PDGF. *See* Platelet-derived growth factor (PDGF)
- PDSA cycle, **261**
- Pearson correlation coefficient (*r*), 253
- Peau d'orange, 616
- Pectinate line, **351**
- Pediatric patients
  - aspirin use for, avoiding, 373
  - common causes of death, 260
  - common fractures, 424
  - cystic fibrosis, 56
  - dactinomycin for, 418
  - disorders of, 527
  - hemolytic-uremic syndrome, 405
  - intussusception in, 368
  - juvenile polyposis syndrome in, 370
  - Munchausen syndrome by proxy, 536
  - nephrotic syndrome in, 566
  - neuroblastomas in, 325
  - precocious puberty in, 53, 318
  - primary brain tumors, **498**
  - rashes, 179
  - rhabdomyomas in, 301
  - scalded skin syndrome, 451
  - sleep terror disorder in, 538
  - strawberry hemangiomas in, 450
  - tetracycline side effects, 188
  - unvaccinated, 182
  - Wilms tumors in, 569
- Pegloticase, 457, 661
- Pegvisomant, 333
- Pellagra
  - vitamin B$_3$ deficiency, 63
- Pelvic inflammatory disease (PID), **181**
  - *Actinomyces*, 135
  - chlamydia, 146, 180
  - *Chlamydia trachomatis*, 146
  - copper IUD, 622
  - ectopic pregnancy, 607
  - gonococci, 138
  - gonorrhea, 180
- Pelvic pain
  - endometriomas, 610
  - endometriosis, 613
- Pelvis
  - fracture and nerve injury, 430
  - nerve injury with surgery, 430
- Pemphigus vulgaris, 452
  - acantholysis and, 448
  - autoantibody with, 111
  - labs/findings, 657
  - type II hypersensitivity, 108
- Penicillamine
  - for copper toxicity, 239
  - for lead poisoning, 239
  - membranous nephropathy and, 566
  - myopathy, 241
  - for Wilson disease, 378
- Penicillin
  - *Actinomyces* spp, 135
  - antipseudomonal, 184
  - Coombs-positive hemolytic anemia, 241
  - mechanism (diagram), 183
  - penicillinase-resistant, 184
  - penicillinase-sensitive, 184
  - prophylaxis, 194
  - rash, 241
  - for rheumatic fever, 300
  - *Treponema pallidum*, 664
- Penicillinase-resistant penicillins, **184**
- Penicillinase-sensitive penicillins, **184**
- Penicillin G, V, **183**
  - meningococci, 138
  - prophylaxis, 194
- Penile cancer, 219
- Penis
  - congenital abnormalities, **591**
  - female homolog, 590
  - lymphatic drainage, 591
  - pathology of, **617**
- Pentamidine, 150
- Pentazocine, 520, **521**
- Pentobarbital, 515
- Pentostatin, 410
- PEP carboxykinase, 70
- Pepsin, 357
- Pepsinogen
  - location of, 357
  - somatostatin and, 356
- Peptic ulcer disease, **363**
  - associations, 664
  - cholinomimetic agents and, 232
  - glycopyrrolate for, 233
  - H$_2$ blockers for, 381
  - *Helicobacter pylori*, 142
  - misoprostol for, 382
  - proton pump inhibitors for, 381
  - Zollinger-Ellison syndrome, 338
- Peptidoglycan synthesis, 183
- *Peptostreptococcus* spp
  - alcoholism, 175
  - lung abscessesy, 646
- Perforation, caused by ulcers, 363
- Perforin
  - cytotoxic T cells and, 98
  - extrinsic pathway and, 204
  - natural killer cells and, 97
- Performance anxiety, 537
- Perfusion, and ventilation, 634
- Perfusion-limited gas exchange, 633
- Periarteriolar lymphatic sheath (PALS), 94
- Pericardial cavity, 271
- Pericardial effusion, 647
- Pericardial tamponade
  - labs/findings, 658
- Pericarditis
  - acute, **300**
  - fibrinous, 294
  - jugular venous pulse in, 276
  - Kussmaul sign in, 301
  - picornaviruses, 163
  - postinfarction, 294
  - pulsus paradoxus in, 300
  - renal failure, 571
  - rheumatoid arthritis, 439
- Pericardium, 271
- Perinephric abscesses, 570
- Perineurium, 465
- Periodic acid-Schiff stain, 122
  - glycogen storage diseases, 83
- Periorbital edema
  - nephrotic syndrome, 655
  - *Trichinella spiralis*, 157
- Peripartum cardiomyopathy, 297
- Peripheral edema
  - calcium channel blockers, 304
  - cirrhosis as cause, 372
  - left heart failure, 298
  - nephrotic syndrome, 655
- Peripheral nerves, **465**
- Peripheral nervous system (PNS), **229**
  - embryologic derivation, 581
  - origins of, **460**
- Peripheral neuropathy
  - alcoholism, 541
  - Chédiak-Higashi syndrome, 113
  - epilepsy drugs, 514
  - Fabry disease, 84
  - isoniazid, 193
  - Krabbe disease, 84, 494
  - NRTIs, 199
  - oxazolidinones, 189
  - sorbitol as cause, 77
  - tricyclic antidepressants, 545
  - vincristine as cause, 422
  - vitamin B$_6$ deficiency, 63
- Peripheral resistance, 235
- Peripheral vascular disease, 292
- Peripheral vertigo, 503
- Periplasm, 120
- Perirenal space, 345
- Peristalsis
  - motilin receptor agonists and, 356
  - visible waves of, 345
- Peritoneum, 345
  - hernias and, 355
- Peritonitis
  - appendicitis, 366
  - diverticulitis, 366
  - spontaneous bacterial, 373
- Peritubular capillaries, 553
- Perivascular rosettes, 498
- Permanent cells, 42
- Permethrin, 157, 196
- Permissive drug interactions, 225
- Pernicious anemia
  - autoantibody with, 111
  - B$_{12}$ deficiency caused by, 398
  - HLA-DR5 and, 96
  - type IV hypersensitivity, 109
  - vitamin B$_{12}$ deficiency, 65
- Peroxisome, **43**
- Persistent cervical sinus, 586
- Persistent depressive disorder, 531
- Persistent fetal circulation, 599
- Persistent thyroglossal duct, 312
- Persistent truncus arteriosus, 269, 288
- Personality, **534**
- Personality disorder, 534
- Personality disorders, **535–536**
- Personality traits, 534
- Pertussis toxin, 128, 139
- Pes cavus
  - Charcot-Marie-Tooth disease, 494
  - Friedreich ataxia, 501
- Petechiae
  - aplastic anemia as cause, 399
  - cirrhosis as cause, 372
  - scurvy, 656
- Petechial rash
  - fat emboli as cause, 637
- Peutz-Jeghers syndrome, 216, 370
- Peyer patches, 347, **358**
  - IgA antibody production, 101
  - intussusception and, 368
  - *Salmonella*/*Shigella* invasion, 141
- Peyronie disease, 617
- PGI$_2$, 455
- P-glycoprotein, **220**
- Phagocytes, 113
- Phagocytosis, 125
- Pharmacokinetics, **225**
- Pharmacology, **224–243**
  - autonomic drugs, 229–238
  - cardiovascular, 304–310
  - endocrine, 340–342
  - gastrointestinal, 381–383
  - hematologic/oncologic, 413–421
  - musculoskeletal/skin/connective tissue, 455–457
  - neurology, 514–521
  - pharmacodynamics, 226–228
  - pharmacokinetics, 224–225
  - psychiatric, 542–546
  - renal, 574–577
  - reproductive, 620–623
  - respiratory, 648–649
  - toxicities and side effects, 239–242
  - USMLE Step 1 preparation for, 265
- Pharyngitis
  - adenoviridae, 160
  - *Corynebacterium diphtheriae*, 135
  - diptheria, 135
  - mononucleosis, 161
  - prophylaxis (rheumatic fever), 194
  - *Streptococcus pyogenes*, 132
  - unvaccinated children, 182
- Pharynx, 628
  - blood supply and innervation of, 348
- Phenacetin, 569
- Phenelzine, 546
- Phenobarbital, 515
  - cytochrome P-450 and, 243
  - epilepsy, 514
  - teratogenicity, 582
  - as weak acid, 226
- Phenotypic mixing, 158

Phenoxybenzamine, 236. *See also* α-antagonists
  norepinephrine and, 228
  for pheochromocytomas, 326
Phentolamine, 236
Phenylalanine
  classification of, 77
  tyrosine catabolism, 79
Phenylbutyrate, 78
Phenylephrine, 234, **648**
  α-blockade of, 236
Phenylketones, 80
Phenylketonuria, 79, **80**
Phenytoin
  cytochrome P-450 and, 243
  drug-induced SLE, 657
  epilepsy, 514
  erythema multiforme, 452
  folate deficiency caused by, 398
  gingival hyperplasia, 241
  lupus-like syndrome, 241
  megaloblastic anemia, 241
  teratogenicity, 582
  tonic-clonic seizures, 663
  vitamin B_9 deficiency, 64
  zero-order elimination of, 226
Pheochromocytomas, **326**
  MEN 2A/MEN 2B and, 339
  neurofibromatosis, 495
  phenoxybenzamine for, 236
  polycythemia and, 217
  presentation, 652
  von Hippel-Lindau disease, 495
Philadelphia chromosome, 668
  in myeloproliferative disorders, 411
  translocations of, 412
Phlebitis
  IV amphotericin B, 195
Phlebotomy, 378
Phobias, 532, **533**
Phocomelia, 582
Phosphatases, 69
Phosphate in bone disorders, 437
Phosphoenolpyruvate carboxykinase, 74
Phosphofructokinase-1 (PFK-1)
  glycolysis and, 69
  metabolic pathways, 70
Phospholipase A_2
  autoantibody to, 111
Phospholipids, 358
Phosphorus in Paget disease of bone, 436
Phosphorylases, 69
Phosphorylation, 41
Photophobia
  headaches, 488
  leptospirosis, 142
  rabies, 167
Photosensitivity
  demeclocycline causing, 342
  drugs causing, 241
  lupus, 443
  porphyria as cause, 403
Photosensitivity (cutaneous)
  simeprevir, 200
  sulfonamides, 190
  tetracyclines, 188
Phototherapy for jaundice, 376
Phrenic nerve, 629
Phyllodes tumors, 614, 615
Physical abuse (child), 526
Physician-assisted suicide, 256
Physiologic dead space, **630**, 670
Physiologic neonatal jaundice, **376**
Physiology
  cardiovascular, 272–286
  endocrine, 314–322
  gastrointestinal, 356–360
  hematolic/oncologic, 389–393
  neurological, 463–485
  renal, 551–562
  reproductive, 595–602
  respiratory, 630–635
  USMLE Step 1 preparation for, 264
Physostigmine
  anticholinergic toxicity treatment, 239
  anticholinesterase, 232
  glaucoma, 521
Pick bodies, 490, 660
Pick disease, 490
Pickwickian syndrome, 642
Picornaviruses, **164**
  characteristics, 163
  genomes, 159
  naked viruses, 159
Pierre Robin sequence, 587
Pigmented skin disorders, **448**
Pigment-producing bacteria, **125**
Pigment stones, 379
Pilocarpine, 232
  glaucoma, 521
Pilocytic astrocytoma, 498
Pilus, 120
Pimozide, 527, 542
Pindolol, 237, 305
Pineal gland, 475
Pinealoma, 498
Pinworms, 155
Pioglitazone, 340
Piperacillin
  characteristics of, 184
  mechanism (diagram), 183
  Pseudomonas aeruginosa, 139
Piroxicam, 456
Pisiform bone, 426
Pitting edema, 298
Pituitary adenomas, **332**, 496
  acromegaly and, 333
  GH and, 317
  goiter and, 327
  hypopituitarism, 335
Pituitary apoplexy, 335
Pituitary drugs, **342**
Pituitary gland, **313**
Pituitary hormones, 244
Pituitary prolactinomas, 315
Pituitary tumors
  diabetes insipidus, 334
  MEN 1 and, 339
Pityriasis rosea, 453
Pityrosporum spp, 148
PKD genes
  renal cyst disorders and, 573
Placebo, 246
Placenta, **584**
  estrogen production, 595
  maternal-fetal barrier, 466
  progesterone production, 595
Placenta accreta/increta/percreta, 606
Placental abruption, 606
  cocaine use, 582
  diffuse cortical necrosis (renal), 570
  preeclampsia, 608
Placental aromatase deficiency, **604**
Placental insufficiency
  oligohydramnios and, 607
  Potter sequence, 548
  preeclampsia, 608
Placenta previa, 606
Plague, 144
Plantar reflex, 480
Plaques (skin), 447
Plasma cells, **389**
Plasma membrane
  cell trafficking, 43
  sodium-potassium pump, 45
Plasma osmolality
  DI treatment, 334
  insulin deficiency/insensitivity, 336
Plasmapheresis, 493, 564
Plasma protein concentration, 553
Plasminogen, 392
Plasmodium spp
  chloroquine, 196
  Giemsa stain for, 122
Plasmodium falciparum, **153**, 196
Plasmodium malariae, **153**
Plasmodium ovale, **153**
Plasmodium vivax, **153**
Platelet-activating factor, 386
Platelet-derived growth factor
  in wound healing, 211
  signaling pathways for, 322
Platelet disorders, **405**
Platelet plug formation, **393**
Platysma muscle, 587
Pleiotropy, **52**
Pleomorphic adenomas, 359
Pleomorphic bacteria, 121
Pleural effusion, **644**
  lung cancer, 647
  mesothelioma, 641
  physical findings, 643
Pleuritis, 439
Plicae circulares, 347
Plummer-Vinson syndrome, 360, 396
Pneumatosis intestinalis, 369
Pneumococcal vaccine, 124
Pneumoconioses, 639, **641**
Pneumocystis spp, 113
Pneumocystis jirovecii, **150**
  dapsone, 190
  HIV-positive adults, 173
  immunocompromised patients, 175
  silver stain for, 122
  TMP-SMX, 190
Pneumocystis pneumonia
  HIV-positive adults, 173
  prophylaxis, 194
Pneumocytes, 626, 627, 628
Pneumonia, **645**
  acute respiratory distress syndrome, 642
  adenoviridae, 160
  chlamydiae, 146
  coccidioidomycosis, 147
  common causes, 175
  compliance in, 631
  Haemophilus influenzae, 138
  inhalational injury, 640
  Klebsiella pneumoniae, 655
  Mycoplasma pneumoniae, 146
  Pneumocystis jirovecii, 150
  proton pump inhibitors and, 381
  Pseudomonas aeruginosa, 139
  Q fever, 145
  readmissions with, 261
  Staphylococcus aureus, 131
  Streptococcus pneumoniae, 132
  Streptococcus agalactiae, 133
  VZV, 160
Pneumonitis
  as granulomatous disease, 211
  HIV-positive adults, 173
Pneumothorax, 643, **644**
Podagra
  gout, 440
  presentation, 656
Podocytes, 550
  in filtration, 553
  glomerular filtration barrier and, 551
  nephrotic syndrome, 566
Poikilocytosis, 386
Point of Service, 259
pol gene, 171
Poliomyelitis, 500, **501**
  restrictive lung disease, 639
  vaccine for, 107
Poliovirus, 501
  immunodeficient patients, 114
  medical importance, 163
  picornavirus, 164
  unvaccinated children, 182
Polyadenylation signal, 38
Polyarteritis nodosa, 169, **302**
  necrosis and, 205
Polyarthralgias
  gonococcal arthritis, 441
  rubella, 178
Polyarthritis
  rheumatic fever, 132
  rubella, 178
Polycystic ovarian syndrome (PCOS), **609**
  anovulation, 609
  antiandrogens, 623

  endometrial hyperplasia, 612
  ovarian neoplasms, 610
Polycythemia, **411**
  blood oxygen in, 633
  bronchitis and, 638
  Eisenmenger syndrome, 289
  ESR in, 212
  hepatocellular carcinoma as cause, 375
  low birth weight, 599
  paraneoplastic syndrome, 216
  presentation, 652
  renal cell carcinoma, 568
Polycythemia vera, 411
  Budd-Chiari syndrome and, 375
Polydactyly, 59
Polydipsia, 336
Polyenes, 194
Polyethylene glycol, 383
Polyhydramnios, 461, 607
  esophageal atresia as cause, 344
Polymenorrhea, 597
Polymerase chain reaction (PCR), **48**
Polymyalgia rheumatica, **444**
  associations, 668
  ESR in, 212
  giant cell arteritis and, 302
Polymyositis, **445**
Polymyxin B, 139
Polymyxins, 194
Polyneuritis, 62
Polyneuropathy, 403
Polyomaviruses
  characteristics of, 160
  DNA viruses, 159
  genome, 158
  naked viruses, 159
Polyostotic fibrous dysplasia, 53, 652
Polyposis syndromes, **370**
Polyps (endometrial), 612
Polyuria
  diabetes insipidus, 334
  diabetes mellitus, 336, 337
  Fanconi syndrome, 655
  hyperosmolar hyperglycemia state, 338
  hyperparathyroidism, 332
  lithium as cause, 544
Pompe disease, 83
Pons, 460, 474
Pontiac fever, 139
"Pope's blessing" (median nerve injury), 427, 429
Popliteal artery, 432
  atherosclerosis in, 292, 668
Popliteal fossa, 432
Popliteal lymph nodes, 93
Porcelain gallbladder, 379
Porphobilinogen deaminase, 403
Porphyria, **403**, 515
Porphyria cutanea tarda, 403
Porphyrin derivatives, 79
Portal hypertension, **372**
  ARPKD, 573
  pulmonary arterial hypertension, 643
  Schistosoma spp, 157
  serum markers for, 373
  varices and, 350
Portal triad, 346, 352
Portal vein, 346, 352
  in fetal circulation, 270
Portal vein thrombosis, 372
Portosystemic anastomoses, **350**
Port-wine stain of face, 495, 656
Positive predictive value (PPV), 247, 249, 669
Positive reinforcement, 524
Positive skew distribution, 251
Postcapillary venule (lymph node), 92
Posterior cerebral artery, 472, 473, 485
Posterior chamber (eye), 504
Posterior circumflex artery, 432
Posterior communicating artery, 473
Posterior cruciate ligament (PCL) injury, 424
Posterior descending artery (PDA), 271
Posterior drawer sign, 424
Posterior fossa malformations, **462**
Posterior hypothalamus, 466
Posterior inferior cerebellar artery
  circle of Willis, 473
  stroke effects, 484
Posterior pituitary gland, 313
Posterior superior pancreaticduodenal arteries, 349
Posterior tibial artery, 432
Posterior urethral valves, 549
Posterior uveitis, 506
Postoperative ileus, 232
Postpartum blues, 532
Postpartum depression, 532
Postpartum hemorrhage, 607
Postpartum mood disturbances, **532**
Postpartum psychosis, 532
Postrenal azotemia, 571
Posttranslational modifications, **41**
Post-traumatic stress disorder (PTSD), 532, **534**
  dissociative identity disorder, 528
  drug therapy for, 542
  prazosin for, 236
  SSRIs for, 545
  venlafaxine, 545
Postural hypotension
  midodrine for, 234
  trazodone, 546
Postviral infections, 175
Potassium
  amphotericin B, 195
  in cardiac muscle, 280
  diabetic ketoacidosis, 337
  PTH and, 320
  shifts in, **560**
  torsades de pointes and, 283
Potassium channel blockers, **309**
Potassium channels
  meglitinides and, 341
  myocardial action potential, 280
  opioid effect, 520
  sulfonylurea effect on, 340
Potassium chloride, 240
Potassium iodide
  Sporothrix schenckii, 150
  for thyroid storm, 329
Potassium-sparing diuretics, 574, **576**
Potency of drugs, vs efficacy, 227
Pott disease, 176
Potter sequence, **548**, 581, 607
  ARPKD, 573
Potter syndrome, 626
Poxviruses
  characteristics of, 160
  DNA viruses, 159
  molluscum contagiosum, 451
PPAR-γ, 341
PPAR-γ activators, 244
PPD test, 136
Practice tests, 19
Prader-Willi syndrome
  chromosome association, 60
  ghrelin in, 317, 356
  imprinting, 54
Pralidoxime, 232
Pramlintide, 240, 341
Prasugrel, 393, 415
Pravastatin, 306
Praziquantel
  antihelminthic therapy, 196
  tapeworms, 156
  trematodes, 156
Prazosin, 236
Precision vs accuracy, 249
Precocious puberty
  adrenal steroids and, 318
  leuprolide, 621
  McCune-Albright syndrome, 53, 652
Precontemplation stage, 539
Prednisolone
  arachidonic acid pathway, 455
  for thyroid storm, 329
Prednisone
  arachidonic acid pathway, 455
Preeclampsia, 608
  hydatidiform moles, 605
  placental abruption, 606
Preferred Provider Organization, 259
Prefrontal cortex, 471
Pregnancy, **598**
  advanced maternal age, 59
  amniotic fluid abnormalities, **607**
  anemia caused by, 396
  carpal tunnel syndrome and, 426
  choriocarcinomas and, 605
  complications of, **606–607**
  contraindicated antimicrobials, **201**
  diabetes in. *See* Gestational diabetes mellitus (GDM)
  ESR in, 212
  estrogen in, 595
  ethical situations, 256–257
  fetal circulation, 270
  fetal hemoglobin, 631
  fetal respiration, 626
  fibroid tumors in, 612
  folate deficiency caused by, 398
  folic acid supplementation, 64
  heparin in, 413
  hypertension in, **608**
  hypertension treatment in, 235, 304
  hypothyroidism in, 328
  insulin in, 314
  Listeria monocytogenes in, 135
  lithium in, 288, 290
  maternal phenylketonuria, 80
  melasma in, 448
  normal urine changes in, 554
  ovarian neoplasms and, 610
  parental consent and, 254
  prolactin and, 316
  propylthiouracil in, 341
  pyelonephritis and, 570
  pyogenic granulomas and, 450
  Rh factor in, 390
  SHBG and, 322
  stillbirth, 178
  Streptococcus agalactiae in, 133
  syphilis in, 143
  termination of, 622
  ToRCHeS infections, 178
  Turner syndrome and, 603
  twinning in, 583
  urinary tract infections, 177
  vitamin B_9 deficiency, 64
Pregnancy-induced hypertension, 608
Pregnenolone, 318
Preload in cardiac output, 273
Premature ejaculation, 545
Premature labor and delivery
  cryptorchidism and, 617
  low birth weight caused by, 599
  murmur in prematurity, 279
  neonatal respiratory distress syndrome and, 627
  smoking, 582
Premature ovarian failure, 609
Premenstrual dysphoric disorder (PMDD), 545
Premotor cortex, 471
Prepatellar bursitis, 425
Preprocollagen, 46
Preproinsulin, 314
Prepuce, 593
Prerenal azotemia, 571
Presbycusis, 259
Presbyopia, 504
Presenilin, 490
Pressors, 299
Pressure-volume loops, **276**
Pretectal nuclei, 509
Preterm birth
  common cause of death, 260
Pretest probability, 247
Prevalence
  diagnostic test evaluation, 247
  incidence vs, 249
  observational studies, 246
  relative risk, 248
Prevotella spp, 175
Priapism, **617**
  sickle cell anemia, 400
  trazodone and, 546

Primaquine, 153
  hemolysis in G6PD deficiency, 241
Primary adrenal insufficiency, **324**
Primary amyloidosis, 659
Primary biliary cirrhosis
  autoantibody with, 111
  as granulomatous disease, 211
  labs/findings, 657
Primary central nervous system lymphoma (PCL), 408
Primary glomerular disease, 563
Primary hemostasis, **393**
Primary hyperaldosteronism, 324
  hypertension with, 290
  markers in, 560
Primary hyperparathyroidism, 331, 332
Primary hypertension, 304
Primary hypogonadism, 604
Primary hypoparathyroidism, 331
Primary sclerosing cholangitis, **378**
  ulcerative colitis, 365
Primary spontaneous pneumothorax, 644
Primase, **35**
Primidone, 489
Primitive atrium, 268
Primitive pulmonary vein, 268
Primitive reflexes, **480**
Primitive ventricle, 268
Pringle maneuver, 346
PR interval, 284
Prinzmetal angina
  calcium channel blockers for, 304
  ischemic manifestations, 293
  propranolol adverse effects, 309
Prions, **174**
Privacy and confidentiality, 255
Probenecid, 243
  cidofovir with, 198
  for gout, 661
  gout, 457
Procainamide, 308
  lupus-like syndrome, 241
Procaine, 519
Procarbazine, 242
Procedure bias, 250
Process (quality measurement), 261
Processus vaginalis, 591
Procoagulation, 392
Progesterone, **595**
  granulosa cell tumors, 611
  lactation and, 599
  menstrual cycle, 597
  ovulation, 596
  pregnancy, 598
  signaling pathways for, 322
Progestin, **622**
  contraception, 622
  endometriosis, 613
Progressive multifocal leukoencephalopathy (PML), 464, 494
  HIV-positive adults, 173
  polyomaviruses, 160
  rituximab, 420
Proguanil, 196
Projection, 525
Prokaryotes
  DNA replication in, 35
  RNA polymerases in, 38
Prolactin, **316**
  circadian rhythm, 467
  lactation and, 599
  pregnancy, 598
  secretion of, 313, 315
  signaling pathways for, 322
  tuberoinfundibular pathway, 468
Prolactinomas
  dopamine agonists for, 316
  pituitary adenomas, 332
Proliferative glomerular disorders, 563
Prometaphase, 42
Promoters (gene expression), **38**
Promyelocytic leukemia, 62
Pronephros, 548
Proopiomelanocortin, 313
Propafenone, 308
Propanolol, 329
Proper hepatic artery, 346
Prophase, 42
Propionibacterium spp, 121
Propionibacterium acnes, 449
Propionyl-CoA carboxylase
  metabolic pathways, 70
  vitamin B_7 and, 64
Propofol, 519
Propranolol, 237, 309
  essential tremor, 489
Proprioception
  Friedreich ataxia, 501
Propylthiouracil
  agranulocytosis, 241
  aplastic anemia, 241
  as inhibitor, 321
  thionamides, 341
  for thyroid storm, 329
Prosencephalon, 460
Prostacyclin, 455
Prostaglandin analogs, 244
Prostaglandins
  arachidonic acid pathway, 455
  aspirin effects, 456
  cortisol effect on, 319
  glaucoma, 521
  kidney functions, 559
  PDA and, 270
Prostate cancer
  adenocarcinomas, **619**
  estrogens for, 621
  incidence/mortality of, 216
  leuprolide for, 621
  metastases of, 221
  tumor suppressor genes and, 218
Prostate gland, 593
  female homolog of, 590
  lymphatic drainage of, 591
Prostatic acid phosphatase (PAP), 619
Prostatitis, **619**
  gonorrhea, 180
Prosthetic devices
  osteomyelitis, 176
  Staphyloccus epidermidis, 131
Prosthetic heart valves, 401
Protamine sulfate, 239, 413
Protease inhibitors
  acute pancreatitis, 380
  fat redistribution, 241
  HIV therapy, 199
  hyperglycemia, 240
  mechanism (diagram), 197
  naming convention for, 244
Proteases, 358
Proteasome, **43**
Protein A, 125
Proteinases, 386
Protein C/S deficiency, 406
Protein kinase A
  fructose bisphosphatase-2 and, 72
  glycogen regulation, 81
Protein metabolism, 70
Protein phosphatase, 81
Proteins
  free radical effect on, 210
Protein synthesis, **41**, 183, 197
  insulin and, 314
  metaboilic site, 68
Protein synthesis inhibitors, **187**, 244
Proteinuria
  ACE inhibitors for, 577
  angiotensin II receptor blockers, 577
  diabetes mellitus, 336
  nephritic syndrome, 564
  nephrotic syndrome, 563, 566, 655
  preeclampsia, 608
  serum sickness, 109
Proteolysis
  cortisol and, 319
  in insulin deficiency, 336
Proteus spp
  Gram-negative algorithm, 137
  nosocomial infection, 181
  taxonomy, 121
  urease-positive, 124
Proteus mirabilis
  cephalosporins, 185
  kidney stones, 567
  penicillins for, 184
  urinary tract infections (UTIs), 177, 570
Prothrombin
  warfarin effect on, 414
Prothrombin gene mutation, 406
Protofilament, 44
Proton pump inhibitors, **381**
  acute interstitial nephritis, 572
  Beers criteria, 238
  gastrin and, 356
  for *Helicobacter pylori*, 142
  naming convention for, 244
Protozoa
  CNS infections, 152
  GI infections, 151
  hematologic infections, 153
  miscellaneous, 154
  watery diarrhea, 175
Proximal convoluted tubules
  defects in, 556
  diuretics and, 574
  dopamine secretion by, 559
  glucose clearance and, 554
  ischemia susceptibility, 206
  physiology of, 555
  relative concentrations in, **557**
  renal cell carcinoma and, 568
  renal tubular acidosis of, 562
Proximal interphalangeal (PIP) joints, 429
PRPP (glutamine-phosphoribosylpyrophosphate) amidotransferase, 69
Pruritus
  anal, 155
  biliary tract disease, 378
  chloroquine, 196
  cutaneous mycoses, 148
  ectoparasites, 157
  histamine receptors and, 230
Prussian blue stain, 641
Psammoma bodies, **220**
  diseases with, 660
  mesotheliomas, 641
  papillary thyroid carcinoma, 330
  serous cystadenocarcinomas, 611
PSA (prostate-specific antigen), 220
Pseudoappendicitis, 141
Pseudocyst, 380
Pseudoephedrine, **648**
Pseudoglandular lung development, 626
Pseudogout, 440
  labs/findings, 660
Pseudohermaphrodites, 604
Pseudohyperaldosteronism
  Cushing syndrome and, 323
Pseudohypoparathyroidism, 331
Pseudomembranous colitis
  clindamycin, 188
  Clostridium difficile, 134
  as drug reaction, 240
  penicillins, 184
  spore-forming bacteria, 127
  vancomycin for, 186
  watery diarrhea, 175
Pseudomembranous pharyngitis
  diptheria, 135
Pseudomonas spp
  catalase-positive organism, 124
  ceftazidime, 185
  cystic fibrosis, 56, 175
  fluoroquinolones, 191
  Gram-negative algorithm, 137
  as nosocomial infection, 175
  osteomyelitis, 176
  penicillins for, 184
  taxonomy, 121
  tricuspid valve endocarditis, 299
  type III secretion system, 125
Pseudomonas aeruginosa, **139**
  aerobic organism, 123
  biofilm production, 125
  encapsulated, 124
  exotoxin production, 128
  immunodeficient patients, 114
  multidrug-resistant, 194
  nosocomial infection, 181

  pigment production, 125, 139
  pyocyanin of, 105
  splenic dysfunction and, 94
  UTIs, 177
Pseudo-Pelger-Huet anomaly, 409
Pseudopseudohypoparathyroidism, 331
Pseudotumor cerebri, **491**
  acetazolamide for, 575
  vitamin A toxicity, 62
Pseudovirion, 158
Psittacosis, 144
Psoriasis, 449
  arthritis and, 442
  cyclosporine, 116
  etanercept for, 457
  hyperkeratosis/parakeratosis, 448
  infliximab/adalimumab for, 457
  methotrexate for, 417
  skin lesions, 447
  therapeutic antibodies, 118
Psoriatic arthritis, 442
  HLA-B27 and, 96
  leflunomide for, 456
  psoriasis and, 449
Psychiatry, 524–546
  pathology, 526–540
  pharmacology, 542–546
  psychology, 524–525
Psychoactive drug intoxication and withdrawal, **540–541**
Psychology, 524–525
Psychosine, 494
Psychosis, **529**
  corticosteroids, 116
  diabetic ketoacidosis, 337
  drug therapy for, 543
  LSD and, 541
  lupus, 443
  PCP and, 541
  postpartum, 532
Psychotherapy
  anorexia/bulimia nervosa, 537
  anorexia nervosa, 661
  conduct disorder, 527
  oppositional defiant disorder, 527
Psychotic disorders
  readmissions with, 261
Psyllium, 383
PTEN gene, 218
Pterygoid muscles, 587
PTH. *See* Parathyroid hormone
PTH-independent hypercalcemia, 331
PTH-related peptide (PTHrP), 320
PTHrP (parathyroid hormone-related protein), 217
Ptosis (eyelids)
  CN III damage, 511
  Horner syndrome, 509, 655
  myasthenia gravis, 445
  Pancoast tumor, 646
Puberty
  GH secretion in, 317
  GnRH and, 315
  Kallmann syndrome and, 604
  precocious, 53, 318
  Tanner stages, 602
Public health sciences, **246–263**
Pudendal nerve, 431
Pulmonary anthrax, **133**
Pulmonary arterial hypertension (PAH), 643
  high altitude and, 635
Pulmonary artery, 586
  fetal circulation, 270
Pulmonary artery stenosis, 290
Pulmonary capillary wedge pressure (PCWP), 286, 634
Pulmonary circulation, **633**
Pulmonary edema
  acute respiratory distress syndrome as cause, 642
  compliance in, 631
  consolidation in, 643
  left heart failure, 298
  loop diuretics for, 575
  LV failure, 296
  mannitol, 575
  nitrates for, 305
  opioids for, 520
  renal failure, 571
Pulmonary embolism, **637**
  deep venous thrombosis and, 636
  direct factor Xa inhibitors for, 415
  heparin for, 413
  obstructive shock, 299
  respiratory alkalosis, 561
  tamoxifen/raloxifene and, 421
  thrombolytics for, 415
Pulmonary fibrosis
  amiodarone and, 309
  bleomycin, 418
  busulfan, 418
  compliance in, 631
  diffusion in, 633
  as drug reaction, 242
  methotrexate, 417
  restrictive lung disease, 639
Pulmonary hemorrhage, 133
Pulmonary hypertension, **643**
  cor pulmonale, 633
  drug therapy, **648**
  PDE-5 inhibitors for, 623
  Schistosoma, 156
  sleep apnea, 642
Pulmonary hypoplasia, 626
  Potter sequence, 548
Pulmonary Langerhans cell histiocytosis, 639
Pulmonary surfactant
  club cells, 627
  compliance and, 631
  NRDS, 627
Pulmonary trunk, 268
Pulmonary vascular resistance (PVR), **634**, 670
  chest wall and, 631
Pulmonic regurgitation, 278
Pulmonic stenosis
  carcinoid syndrome, 338
  systolic ejection murmur in, 278
  wide splitting in, 277
Pulmonic valves, 268
"Pulseless disease," 302
Pulse pressure, 272
Pulsus paradoxus, 300
  asthma, 638
  croup, 166
Punched-out ulcers, 360
Punishment, 524
Pupil
  anatomy, 504
  CN III palsy, 511
  control, 477, **509**
Pure red cell aplasia, 217
Purines, 190
  de novo synthesis, 33
  salvage deficiencies, **34**
Purkinje cells
  of cerebellum, 206, 469
  in paraneoplastic cerebellar degeneration, 217
Purkinje fibers, 282
Purpura
  aplastic anemia, 399
  cirrhosis, 372
Pustular psoriasis, 447
Pustules, 447
Putamen, 470
  neurodegenerative disorders, 490
Pyelonephritis, **570**
  kidney stones, 567
  labs/findings, 660, 661
  urinary tract infections, 177
  WBC casts in, 562
Pygmalion effect, 250
Pyloric sphincter, 357
Pyloromyotomy, 345
Pyoderma gangrenosum
  inflammatory bowel disease, 365
Pyogenic granulomas, 450
Pyramidal cells, 206
Pyramidal decussation, 474
Pyramidalis muscle, 354
Pyrantel pamoate, 196
Pyrazinamide, **193**
  gout, 241
  hepatitis, 240
  Mycobacterium tuberculosis, 192
Pyridostigmine, 232
Pyridoxal phosphate, 63
Pyrimethamine, 33, 196
  Toxoplasma gondii, 663
Pyrimidine dimers, 37
Pyrimidines, 33
Pyrimidine synthesis, 456
Pyruvate carboxylase, 73, 74
  metabolic pathways, 70
  vitamin B_7 and, 64
Pyruvate dehydrogenase
  complex, **72**
  deficiency, **73**
  metabolic pathways, 70
  vitamin B_1 and, 62
Pyruvate kinase, 70
Pyruvate kinase deficiency, 400
  in anemia taxonomy, 396
  echinocytes in, 394
Pyruvate metabolism, **73**
Pyuria, 572

Q

Q fever
  rickettsial disease, **145**
  transmission, 144
QRS complex, 282
QT interval
  atypical antipsychotic effect on, 543
  Class IA antiarrhythmic effects, 308
  congenital long QT syndrome, 283
  drug-induced long, 283
  ECG, 282
  ondansetron effect on, 383
  in torsades de pointes, 283
Quality measurements, **261**
Quantifying risk, 248
Quetiapine, 543
Quiescent cells, 42
Quinidine, 153, 196, 308
  cinchonism, 242
  cytochrome P-450 and, 243
  diarrhea, 240
Quinine, 196
Quinolone, 139, 183
Quinupristin, 183, 194

R

Rabies, **167**
  active and passive immunity, 107
  rhabdovirus, 163
  vaccine, 158
  viral receptors, 162
Radial nerve, 427
Radiation exposure
  acute myelogenous leukemia and, 410
  aplastic anemia, 399
  apoptosis caused by, 204
  as carcinogen, 219
  free radical injury caused by, 210
  hypopituitarism, 335
  myelodysplastic syndromes, 409
Radiation therapy
  acute pericarditis and, 300
  angiosarcomas, 450
  lymphopenia, 402
  for Nelson syndrome, 332
  neutropenia, 402
  osteosarcomas, 438
  pancreatic cancer, 380
  papillary thyroid carcinoma risk, 330
  readmissions with, 261
Radon
  as carcinogen, 219
  lung cancer, 647
Ragged red muscle fibers, 55
Rales, 298
Raloxifene, **421**, 621
Raltegravir, 197, 199
Ramipril, 577
Ranibizumab, 118
  macular degeneration, 506
Ranitidine, 381
RANK-L, 320

- Ranolazine, **305**
- Rapid-eye movement (REM) sleep, 467
- Rapidly progressive glomerulonephritis (RPGN), 564
- Rapid squatting on auscultation, 278
- Rasagiline, **518**
- Rasburicase, 421, 567
- *RAS* gene, 330
- Rashes
  - butterfly, 652
  - carbapenems, 186
  - childhood, 179
  - cytomegalovirus, 178
  - desquamating, 652
  - fluoroquinolones, 191
  - Kawasaki disease, 302
  - lupus, 443
  - macrolides, 189
  - measles, 166
  - nipple/areola, 655
  - palms/soles, 655
  - penicillinase-sensitive penicillins as cause, 184
  - rickettsial diseases, 145
  - rubella, 165, 178
  - simeprevir, 200
  - syphilis as cause, 143, 180
  - unvaccinated children, 182
- Rathke pouch, 313, 498
- Rationalization, 525
- Raynaud phenomenon, **445**
  - Buerger disease, 302
  - calcium channel blockers for, 304
  - CREST syndrome, 446
  - presentation, 655
  - SLE, 652
- Rb, 42
- *Rb* gene, 218
- Reabsorption rate, **554**
- Reaction formation, 525
- Reactive arthritis, **442**
  - *Campylobacter jejuni*, 140
  - chlamydia, 146, 180
  - HLA-B27 and, 96
  - presentation, 656
- Reactive attachment disorder, 526
- Reactive cellular changes, **214**
- Readmission recurrences, 261
- Reassortment (viral), 158, 165
- Recall bias in studies, 250
- Receptor binding, **228**
- Receptors (viral), 162
- Receptor tyrosine kinase
  - hormone messenger, 322
  - as oncogene product, 218
- Recessive inheritance, 55
- Recombinant cytokines, **117**
- Recombination (viral), 158
- Recruiting study participants, 250
- Rectal veins, 350
- Rectum
  - anastomosis at, 350
  - blood supply and innervation, 348
  - familial adenomatous polyposis, 370
  - Hirschsprung disease, 367
  - ischemia susceptibility, 206
- Rectus abdominis muscle, 354
- Recurrent branch of median nerve, 427
- Recurrent laryngeal nerve, 586
- Recurrent laryngeal nerves, 586
- Red cell casts, 302
- Red-green color blindness, 193
- Red infarct vs pale infarct, 207
- Red man syndrome, 186
- Redox reactions
  - free radical injury and, 210
  - vitamin B_2 and, 63
- Red pulp (spleen), 94
- Red rashes of childhood, **179**
- Reduviid bug (disease vector), 154
- Reed-Sternberg cells, 407
- Refeeding syndrome, 537
- Reflex bradycardia, 558
- Reflexes
  - clinical, **480**
  - cranial nerve, **477**
  - motor neuron sign, 499
  - primitive, **480**
- Reflex tachycardia, 236
- Refractive errors (vision), **504**
- Refractory hypertension, 623
- Refusing care, 257
  - minors, 257
- Regadenoson, 293
- Regan-Lowe medium, 123
- Regional specification (brain), **460**
- Registering for exam, 5–6
- Regression, 525
- Regular insulin, 340. *See also* Insulin
- Regulation of gene expression, **38**
- Regulatory T cells, **98**
  - cell surface proteins, 106
- Regurgitation in GERD, 360
- Reheated rice syndrome, 134
- Reichert cartilage, 587
- Reid index, 638
- Reinke crystals, 619, 660
- Relapse stage, 539
- Relapsing fever
  - animal transmission, 144
  - lice, 157
- Relative risk reduction (RRR), 248, 669
- Relative risk (RR), 246, 248, 252, 669
- Reliability, 249
- Religious beliefs, 257
- REM sleep, 467
- Renal artery, 348, 550
  - horseshoe kidney, 549
- Renal blood flow, 550, 670
  - endocrine function and, 559
- Renal cell carcinomas, **568**
  - associations, 668
  - bevacizumab for, 420
  - carcinogens causing, 219
  - chromosome association, 60
  - horseshoe kidney and, 549
  - hypercalcemia and, 217
  - IFN-α for, 200
  - metastases of, 221
  - recombinant cytokines, 117
  - therapeutic antibodies, 118
  - von Hippel-Lindau disease, 495, 655
- Renal clearance, **552**, 670
- Renal cortex, 550
  - hydronephrosis, 568
- Renal cyst disorders, **573**
- Renal disease
  - ESR in, 212
  - lupus, 443
  - maintenance and loading dose in, 225
  - Wilson disease, 378
- Renal drug reactions, **242**
- Renal failure
  - diabetes mellitus, 336
  - Enterotoxigenic *Escherichia coli* (EHEC), 140
  - Fabry disease, 84
  - guanosine analogs, 197
  - labs/findings, 660
  - myoclonus in, 489
  - preeclampsia and, 608
  - prolactin elimination in, 316
  - tetracycline use in, 188
  - vitamin D deficiency, 319
- Renal failure/disorders, **571**
  - consequences of, 571
  - markers for, **560**
  - NSAIDs, 559
  - renal cyst disorders, 573
  - waxy casts in, 562
- Renal hypoxia, 632
- Renal ischemia, 456
- Renal medulla, 550
  - hydronephrosis, 568
- Renal oncocytomas, **568**
- Renal osteodystrophy, 332, 571
- Renal papillary necrosis, **572**
  - pyelonephritis and, 570
  - sickle cell anemia, 400
- Renal pelvis, 550
- Renal plasma flow, 552
  - glomerular dynamics and, 553
- Renal toxicity
  - gancyclovir, 198
- Renal tubular acidosis, **562**
  - Fanconi syndrome, 655
  - metabolic acidosis, 561
- Renal tubules
  - anatomy of, 550
  - defects in, **556**
  - in nephron physiology, 555
  - PTH and, 320
- Renal vascular smooth muscle, 230
- Renal vein, 550
- Renin, 558
  - ACE inhibitor effect on, 577
  - aliskiren effect on, 577
  - in hyperaldosteronism, 324
  - renal disorders and, 560
  - sympathetic receptors and, 230
- Renin-angiotensin, 312
- Renin-angiotensin-aldosterone system, **558**
- Renin secreting tumors, 560
- Renshaw cells, 128, 134
- Reoviruses
  - characteristics, 163
  - genome, 159
  - naked viruses, 159
  - segmented, 164
- Repaglinide, 341
- Reperfusion injury, 207, 294
- Reperfusion therapy, 296
- Replication fork, **35**
- Replication (viral), **159**
- Reportable diseases
  - confidentiality exceptions, 255
- Repression, 525
- Repressor proteins, 36
- Reproductive hormones, **620**
- Reproductive system, 580–621
  - anatomy, 591–594
  - drug reactions in, **240**
  - embryology, 580–591
  - pathology, 603–617
  - pharmacology, 620–623
  - physiology, 595–602
- Reptile (disease vectors), 144
- Rescheduling exam, 6
- Reserpine
  - Huntington disease, 518
  - as noradrenergic drug, 231
  - Parkinson-like syndrome, 242
- Residual volume (RV), 630, 637
- Resistance equation, 670
- Resistance in vessels, **274**
- Respiratory acidosis, 561
- Respiratory alkalosis, 561
  - causes of, 561
  - high altitude, 635
  - pulmonary embolism, 637
- Respiratory burst, **105**
  - free radical injury and, 210
- Respiratory depression
  - barbiturates, 515, 540
  - benzodiazepines, 514, 540
  - epilepsy drugs, 514
  - inhaled anesthetics, 519
  - opioids, 520
  - tricyclic antidepressants, 545
- Respiratory distress syndrome, 599
- Respiratory drug reactions, **242**
- Respiratory rate (RR), 630
- Respiratory syncytial virus (RSV)
  - paramyxovirus, 163, 165
  - pneumonia, 175, 645
  - prophylaxis, 118
  - ribavirin, 200
- Respiratory system, 626–649
  - anatomy, 628–629
  - embryology, 626–627
  - pathology, 636–646
  - pharmacology, 648–649
  - physiology, 630–635
- Respiratory tract infections
  - C3 deficiency, 103
- Respiratory tree, **628**
- Respiratory zone, 628

- Resting tremor, 489, 655
- Restrictive cardiomyopathy, 297
  - amyloidosis and, 213
  - S4 heart sound and, 668
- Restrictive lung diseases, **639**
  - flow volume loops, 637
  - sarcoidosis, 444
- Reteplase, 391, 415
- Rete testis, 593
- *RET* gene, 218
  - carcinoma risks with, 330
  - Hirschsprung disease, 367
  - pheochromocytomas, 326
- Reticular activating system, 481
- Reticular fibrous framework (spleen), 94
- Reticulate bodies, 146
- Reticulin, 46
- Reticulocytes, 386
  - in aplastic anemia, 399
  - intravascular hemolysis, 399
- Retina
  - chronic hyperglycemia, 507
  - degeneration of, 506
  - embryologic derivation of, 581
  - normal eye, 504
  - vascular occlusions, 507
  - visual field defects, 511
  - von Hippel-Lindau disease, 495
- Retinal artery, 504
- Retinal detachment, **507**
- Retinal hemorrhage, 507
  - child abuse sign, 526
  - hypertensive emergency, 290
  - Roth spots, 655
- Retinal vein, 504
- Retinal vein occlusion, **507**
- Retinitis, 506, **508**
  - cidofovir, 198
  - foscarnet, 198
  - HIV-positive adults, 173
- Retinitis pigmentosa, **508**
- Retinoblastoma
  - chromosome association, 60
  - heterozygosity loss, 52
- Retinoblastomas
  - osteosarcomas, 438
  - tumor suppressor genes and, 218
- Retinoids, 449
- Retinopathy
  - Alport syndrome, 565
  - chloroquine, 196
  - diabetes mellitus, 336
  - hypertension, 290
  - of prematurity, 210, 627
  - sorbitol, 77
- Retrognathia, 548
- Retrograde amnesia, 528
- Retroperitoneal fibrosis, 568
- Retroperitoneal structures, **345**
- Retrospective studies, 250
- Retroviruses
  - characteristics, 163
  - genomes, 159
- Rett syndrome, 527
  - X-linked dominant inheritance, 55
- Reverse transcriptase, 171
- Reverse transcriptase inhibitors, 197
- Reye syndrome, **373**
- Reynolds pentad, 379
- Rhabdomyolysis
  - daptomycin, 191
  - hyperkalemia with, 560
- Rhabdomyomas, 301
  - nomenclature for, 216
  - tuberous sclerosis, 495
- Rhabdomyosarcomas
  - dactinomycin for, 418
  - desmin stain for, 44
  - nomenclature for, 216
- Rhabdoviruses
  - characteristics, 163
  - negative-stranded, 164
- Rhagades, 143
- Rh blood classification, 390
- Rheumatic fever, **300**
  - criteria for, 132
  - heart murmur with, 279
  - *Streptococcus pyogenes*, 132
  - streptolysin O, 129
  - type II hypersensitivity, 108
- Rheumatoid arthritis, **439**
  - AA amyloidosis and, 213
  - anemia of chronic disease, 399
  - autoantibody with, 111
  - azathioprine for, 417
  - biliary cirrhosis, 378
  - carpal tunnel syndrome and, 426
  - celecoxib for, 456
  - etanercept for, 457
  - HLA-DR4 and, 96
  - immunosuppressants, 116
  - infliximab/adalimumab for, 457
  - labs/findings, 657
  - leflunomide for, 456
  - methotrexate for, 417
  - rituximab, 118
  - rituximab for, 420
  - uveitis, 506
- Rheumatoid factor, 111
- Rh hemolytic disease of the newborn, **390**
- Rhinitis
  - phenylephrine for, 234
  - type I hypersensitivity, 108
- Rhinosinusitis, **636**
- Rhinovirus
  - picornavirus, 163, 164
  - receptors for, 162
- *Rhizopus* spp, **149**
  - presentation, 652
- RhoGAM, 390
- Rhombencephalon, 460
- Rhomboid crystals, 660
- Ribavirin
  - contraindicated in pregnancy, 201
  - hepatitis, 661
  - hepatitis C, 200
  - purine synthesis, 33
- Rib notching, 660
- Ribose, 75
- Ribosomes, 42
- Rice-water diarrhea
  - cholera toxin, 128
  - organisms causing, 175
  - *Vibrio cholerae*, 141
- Richter transformation, 410
- Rickets, **436**
  - Fanconi syndrome, 655
  - hypophosphatemia, 560
  - inheritance, 55
  - lab values in, 437
  - vitamin D deficiency, 66, 319
- *Rickettsia* spp
  - Giemsa stain for, 122
  - intracellular organism, 124
  - taxonomy, 121
  - tetracyclines, 188
- Rickettsial diseases, **145**
- *Rickettsia prowazekii*, 145
  - transmission of, 144, 157
- *Rickettsia rickettsii*, 145
  - animal transmission, 144
  - chloramphenicol, 188
- *Rickettsia typhi*, 144, 145
- Riedel thyroiditis, 328
- Rifabutin, 192
- Rifamixin, 78
- Rifampin, 192
  - acute interstitial nephritis, 572
  - cytochrome P-450 and, 243
  - Hansen disease, 137
  - hepatitis, 240
  - mechanism (diagram), 183
  - *Mycobacterium leprae*, 192
  - *Mycobacterium tuberculosis*, 192
  - as prophylaxis, 194
  - protease inhibitors and, 199
  - RNA polymerase inhibition, 38
- Rifamycins, **192**
- Rifaximin, 374
- Rift Valley fever, 163
- Right anterior cardinal vein, 268
- Right bundle branch, 282
- Right bundle branch block, 277
- Right common cardinal vein, 268
- Right coronary artery (RCA)
  - coronary circulation, 271
  - infarct localization (ECG), 295
  - occlusions of, 294
- Right external iliac artery, 348
- Right gastroepiploic artery, 349
- Right horn of sinus venosus, 268
- Right inferior phrenic artery, 348
- Right internal iliac artery, 348
- Right lower quadrant (RLQ) pain, 367
- Right lymphatic duct, 93
- Right marginal artery, 271
- Right renal artery, 348
- Right-to-left shunts, 288
- Right upper quadrant (RUQ) pain, 379
- Right ventricular hypertrophy (RVH)
  - high altitude, 635
  - pulmonary hypertension, 643
- Rigidity in Parkinson disease, 655
- Riluzole, **518**
  - amyotrophic lateral sclerosis, 500
- Rimantadine, 197
- Ringed sideroblasts, 395
- Ringworm
  - griseofulvin, 196
  - tinea corporis, 148
- Risedronate, 456
- Risk quantification, **248**
- Risperidone, 530, 543
- Ristocetin, 393
- Risus sardonicus
  - *Clostridium tetani*, 134
  - tetanospasmin, 128
- Ritodrine, **622**
- Ritonavir
  - cytochrome P-450 and, 243
  - HIV therapy, 199
  - mechanism (diagram), 197
- Rituximab, 118, **420**, 494
- Rivaroxaban, 415
  - as anticoagulant, 391
  - deep venous thrombosis, 636
- Rivastigmine, 232
  - Alzheimer disease, 518
- River blindness, 155
- RNA
  - interference, 52
  - processing (eukaryotes), **38**
- RNA polymerases, **38**
- RNA viruses, **163**
  - genome, **159**
  - replication, 159
- Robertsonian translocation, **60**
- Rocker-bottom feet
  - autosomal trisomies, 59
- Rocky Mountain spotted fever, **145**
  - animal transmission, 144
  - chloramphenicol, 188
  - presentation, 655
- Rocuronium, 520
- Rod bacteria, 121
- Romaña sign, 154
- Romano-Ward syndrome, 283
- Romberg sign, 143, 500
- Romiplostim, 117
- Root cause analysis, 262
- Rooting reflex, 480
- Rosacea, 449
- Rose gardener's disease, 150
- Rosenthal fibers, 498
- Roseola
  - HHV-6/HHV-7, 161
  - rash, 179
- Rosiglitazone, 340
- Rostral fold closure defects, 344
- Rosuvastatin, 306
- Rotator cuff muscles, **425**
- Rotavirus, **164**
  - diarrhea, 163, 175
- Rotenone, 74
- Roth spots, 299, 655
- Rotor syndrome, 376, 377
- Rough endoplasmic reticulum, **42**
- Rouleaux formation, 409, 660
- Round ligament of uterus, 592
- Rovsing sign, 366, 656
- Rubella, **165**
  - cardiac defect association, 290
  - cataracts, 505

- Rubella *(continued)*
  - heart murmur with, 279
  - rash, 179
  - ToRCHeS infection, 178
  - unvaccinated children, 182
- Ruffini corpuscles, 464
- Russell sign, 537
- Ryanodine receptor, 433

S

- Saber shins
  - congenital syphilis, 143
  - syphilis, 178
- Sabin poliovirus vaccine, 158, 163
- Sabouraud agar, 123, 149
- Saccular aneurysms, 486
  - Ehlers-Danlos syndrome, 47
  - renal cyst disorders and, 573
- Saccular lung development, 626
- Sacrococcygeal teratomas, 618
- Saddle nose
  - congenital syphilis, 143
  - Laron syndrome, 333
  - syphilis, 178
- Safety culture, **261**
- Salicylates
  - metabolic acidosis, 561
  - respiratory alkalosis, 561
  - toxicity treatment for, 239
- Salivary gland tumors, **359**
- Salivary stimulation, 232
- Salk polio vaccine, 158
- Salmeterol, 234, 649
- *Salmonella* spp
  - animal transmission, 144
  - bloody diarrhea, 175
  - encapsulated bacteria, 124
  - food poisoning, 174
  - Gram-negative algorithm, 137
  - immunodeficient patients, 114
  - intracellular organism, 124
  - osteomyelitis, 176
  - penicillins for, 184
  - reactive arthritiS, 442
  - *Shigella* spp vs, **141**
  - splenic dysfunction, 94
  - taxonomy, 121
  - TMP-SMX for, 190
  - type III secretion system, 125
- *Salmonella typhi*, 141
- Salpingitis
  - ectopic pregnancy and, 607
  - pelvic inflammatory disease, 181
- Sampling bias, 250
- Sandflies (disease vectors), 154
- Sandfly fever, 163
- Saponification, 205
- *Saprophyticus*
  - urease-positive, 124
- Saquinavir, 197, 199
- Sarcoidosis, **444**
  - acute interstitial nephritis, 572
  - cardiomyopathy with, 297
  - erythema nodosum, 453
  - as granulomatous disease, 211
  - hypervitaminosis D, 437
  - macrophages and, 387
  - presentation, 652
  - restrictive lung disease, 639
  - uveitis, 506
- Sarcoma botryoides, 609
- Sarcomas
  - metastases of, 221
  - methotrexate for, 417
  - nomenclature of, 216
  - vimentin stain, 44
- Sarcoplasmic reticulum, 433
- Sargramostim, 117
- SARS (sudden acute respiratory syndrome), 163
- Sartorius muscle, 353
- Saturday night palsy, 427
- Saxagliptin, 341
- Scabies, 157, 196
- Scalded skin syndrome
  - *Staphylococcus aureus*, 131
  - toxic shock syndrome toxin, 129
- Scales (skin), 447
- Scaphoid bone, 426
- Scar formation, 207, **210**
- Scarlet fever
  - presentation, 132, 656
  - rash caused by, 179
  - *Streptococcus pyogenes*, 132
- S cells, 356
- Schiller-Duval bodies, 611
- Schilling test, 398
- Schistocytes, 395
  - HELLP syndrome, 608
  - in intravascular hemolysis, 399
  - in microangiopathic anemia, 401
- *Schistosoma* spp, **156**, 157
- *Schistosoma haematobium*
  - disease association, 156, 157
  - as oncogenic microbe, 219
  - squamous cell carcinoma of bladder, 569
- *Schistosoma mansoni*, 156
- Schistosomiasis
  - as granulomatous disease, 211
  - portal hypertension, 372
  - pulmonary arterial hypertension, 643
- Schizoaffective disorder, 530
- Schizoid personality disorder, 535
- Schizophrenia, **530**
  - antipsychotics for, 543
  - atypical antipsychotics for, 543
  - drug therapy for, 542
  - neurotransmitters for, 465
  - readmissions with, 261
- Schizophreniform disorder, 530
- Schizotypal personality disorder, 535
- Schüffner stippling, 153
- Schwann cells, **464**
  - Guillain-Barré syndrome, 493
  - origin of, 460
- Schwannomas, 464, 496, 664
- Sciatic nerve, 430
- SCID (severe combined immunodeficiency disease), 113
  - adenosine deaminase deficiency as cause, 34
  - lymphopenia caused by, 402
- Sclerae, 504
  - alkaptonuria, 80
  - osteogenesis imperfecta, 47
- Scleritis, 439
- Sclerodactyly, 446
- Scleroderma, **446**
  - autoantibody with, 111
  - labs/findings, 657
- Sclerodermal esophageal dysmotility, 360
- Sclerosing adenosis, 615
- Sclerosing cholangitis, 376, 378
  - ulcerative colitis as cause, 365
- Scombroid poisoning, 238
- Scopolamine, 233
- Scoring of USMLE Step 1 exam, 7, 8–9
- Scorpion sting, pancreatitis caused by, 380
- Scotoma, 511
- Scrotum, 593
  - female homolog of, 590
  - lymphatic drainage of, 591
  - masses in, **618**
- Scurvy
  - collagen synthesis and, 46
  - presentation, 656
  - vitamin C deficiency, 65
- Seafood toxins, **238**
- Seborrheic keratosis, 449
- Sebum, 449
- Secobarbital, 515
- Secondary adrenal insufficiency, 324
- Secondary biliary cholangitis, 378
- Secondary glomerular disease, 563
- Secondary hyperaldosteronism, 324
- Secondary hyperparathyroidism, 331, 332
- Secondary spontaneous pneumothorax, 644
- Secondary syphilis
  - labs/findings, 655
  - presentation, 656
- Second-wind phenomenon, 83
- Secretin
  - regulatory substances, 356
  - secretory cell location, 357
  - somatostatinomas and, 338
- Secretion rate calculation, **554**
- Secretory vesicles, 43
- Segmental artery, 550
- Segmented viruses, **164**
- Seizures, **487**
  - aluminum hydroxide, 382
  - amphetamines, 540
  - Angelman syndrome, 54
  - barbiturates for, 515
  - benzodiazepine withdrawal, 540
  - β-blockers, 237
  - bupropion, 546
  - cytomegalovirus, 178
  - delirium tremens, 542
  - as drug reaction, 242
  - electrolyte disturbances, 560
  - enflurane, 242
  - hyperosmolar hyperglycemia nonketotic syndrome as cause, 338
  - hyperosmolar hyperglycemic state, 342
  - imipenem/cilastatin, 242
  - lupus, 443
  - medium-chain acyl-CoA dehydrogenase deficiency, 85
  - meropenem, 186
  - PCP, 541
  - phenylketonuria, 80
  - serotonin syndrome, 545
  - *Taenia solium*, 157
  - tramadol and, 521
  - tuberous sclerosis, 495
  - vitamin B_6 deficiency, 63
- Selection bias, 250
- Selective estrogen receptor modulators (SERMs), 421, 435, **621**
- Selective IgA deficiency, 112
- Selective media, 122
- Selective serotonin reuptake inhibitors (SSRIs)
  - bulimia nervosa, 661
  - diarrhea, 240
  - naming convention for, 244
  - SIADH caused by, 240
- Selegiline, 517, **518**, 546
- Selenium sulfide, 148
- Self-fulfilling prophecies, 250
- Seminal vesicles, 589, 593
- Seminiferous tubules, 593, **594**, 601
- Seminomas, 618, 668
- Semustine, 418
- Senna, 383
- Sensitivity (diagnostic tests), **247**
- Sensitivity equation, 669
- Sensorineural hearing loss, 503
- Sensory cortex, 484
- Sensory receptors, **464**
- Separation anxiety disorder, 527
- Separation anxiety in infants, 258
- Sepsis
  - acute tubular necrosis, 572
  - ARDS, 642
  - immunodeficient patients, 114
  - lymphopenia with, 402
  - neutropenia with, 402
  - *Pseudomonas aeruginosa*, 139
  - shock with, 299
  - *Streptococcus agalactiae* as cause, 133
- Septate uterus, 590
- Septation of heart chambers, 268
- Septic arthritis, **441**
  - gonococci, 138
  - *Staphylococcus aureus*, 131
- Septicemia
  - *Listeria monocytogenes*, 135
  - readmissions with, 261
  - Waterhouse-Friderichsen syndrome, 324
- Septic shock
  - diffuse cortical necrosis (renal), 570
  - macrophages and, 387
  - norepinephrine for, 234
- Septum primum, 268

Septum secundum, 268
Serine, 218
Seronegative spondyloarthritis, **442**
Serosa, 347
Serositis, 443
Serotonin
  in carcinoid syndrome, 338
  changes with disease, 465
  derivatives of, 79
  vitamin B$_6$ and, 63
Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  fibromyalgia, 444
Serotonin syndrome, 516, 521, **545**
  dextromethorphan, 648
  MAO inhibitors, 546
  MDMA, 541
  oxazolidinones, 189
Serous cystadenocarcinomas, 610, 611
Serous cystadenomas, 610
Serous papillary cystadenocarcinomas of ovary, 220
Serrated colon polyps, **370**
Serratia spp
  catalase-positive organism, 124
  Gram-negative algorithm, 137
  immunodeficient patients, 114
  lactose fermentation by, 138
  taxonomy, 121
Serratia marcescens
  cephalosporins, 185
  pigment production, 125
  UTIs, 177
Serratus anterior muscle, 428
Sertoli cells
  secretions of, 594
  sexual determination, 589
  tumors, 619
Sertraline, 545
Serum amyloid A, 102
Serum lactate, 336
Serum markers of liver pathology, **373**
Serum osmolarity
  antidiuretic hormone regulation of, 317
  hyperosmolar hyperglycemia nonketotic syndrome, 338
Serum sickness, 109
Serum tumor markers, **220**
17α-hydroxylase, 318
Sevoflurane, 519
Sex chromosome disorders, **603**
Sex hormone-binding globulin (SHBG), 322
Sex hormone disorders, **604**
Sex hormones
  adrenal cortex secretion, 312
Sex pilus (bacterial genetics), 126
Sex steroid replacement, 335
Sexual abuse, 528
Sexual abuse (child), 526
Sexual development stages, 602
Sexual dysfunction, **537**
  β-blockers, 237
  β-blockers and, 309
  cimetidine, 381
  Lambert-Eaton myasthenic syndrome, 445
  PDE-5 inhibitors for, 623
  Peyronie disease and, 617
  sildenafil, 648
  tuberoinfundibular pathway, 468
Sexually transmitted infections (STIs), **180**
  associations, 668
  parental consent with, 254
  sexual dysfunction, 537
Sézary syndrome, 408
SGLT-2 inhibitors, 341
Shagreen patches, 495
“Shawl and face” rash, 445
SHBG. *See* Sex hormone-binding globulin (SHBG)
Sheehan syndrome, 335, 606
Sheep (disease vectors), 156
Shield chest, 603
Shiga-like toxin, 128, 140
Shiga toxin, 126, 128, 141
Shigella spp
  bloody diarrhea, 175
  exotoxin production, 128
  penicillinase-sensitive penicillins for, 184
  reactive arthritis, 442
  vs *Salmonella* spp, **141**
  taxonomy, 121
  TMP-SMX, 190
  type III secretion system, 125
Shigella boydii, 141
Shigella dysenteriae, 141
Shigella flexneri, 141
Shigella sonnei, 141
Shingles, 160
Shock, **299**
  acute tubular necrosis, 572
  ARDS, 642
  dopamine for, 234
  Ebola, 167
  endotoxins, 127
  norepinephrine for, 234
  placental abruption, 606
  pulmonary anthrax, 133
  Waterhouse-Friderichsen syndrome and, 324
Short gastric arteries, 349
Shortness of breath, 533
SIADH, **334**
  ADH antagonists for, 342
  associations, 668
  carbamazepine, 240, 514
  cyclophosphamide, 240
  demeclocycline for, 342
  as drug reaction, 240
  markers in, 560
  small cell lung cancer, 647
Sialyl-Lewis^x, 209
Sibling studies, 246
Sickle cell anemia, 400
  in anemia taxonomy, 396
  ESR in, 212
  sickle cells in, 395
Sickle cell disease
  autosplenectomy, 664
  chromosome association, 60
  focal segmental glomerulosclerosis, 566
  missense mutation, 36
  osteomyelitis, 176
  osteonecrosis and, 436
  priapism, 617
  renal papillary necrosis, 572
Sickle cells, 395
Sideroblastic anemia, 395, 397
  in anemia taxonomy, 396
  labs/findings, 657
  lead poisoning, 397
  vitamin B$_6$ deficiency, 63
Sigmoid colon, 366, 668
Sigmoid sinus, 473
Signaling pathways
  endocrine hormones, **322**
  steroid hormones, **322**
Signal recognition particle (SRP), 43
Signet cell adenocarcinomas, 611
Signet ring cells, 362
Sign of Leser-Trélat, 217
Sildenafil, 617, 623
  pulmonary hypertension, 648
Silencers (gene expression), **38**
Silent mutations, **36**
Silicosis, 639, **641**
Silver stain, 122, 139
Simeprevir, 200
  hepatitis, 661
Simple pneumothorax, 643
Simple renal cysts, 573
Simvastatin, 306
Single nucleotide polymorphisms (SNPs), 50
Single-stranded binding proteins, 35
Sinusitis
  brain abscesses, 176
  C3 deficiency and, 103
  Kartagener syndrome, 45, 656
  Wegener granulomatosis, 302
Sinusoids (spleen), **94**
Sinus venosus, 268
Sirolimus
  immunosuppressant, 116
  targets of, 117
Sister Mary Joseph nodules, 362
Sitagliptin, 341
Situs inversus, 45, 656
6-mercaptopurine, 417
  allopurinol and, 457
  azathioprine, 116
  in cell cycle, 416
  purine synthesis, 33
  targets of, 416
  toxicities of, 422
  for ulcerative colitis, 365
  ulcerative colitis, 664
6-thioguanine, 416
Sjögren syndrome, **441**
  acute interstitial nephritis with, 572
  autoantibody with, 111
  biliary cirrhosis and, 378
  pilocarpine for, 232
  rheumatoid arthritis, 439
Skeletal muscles
  ACh receptors in, 229
  autoregulation of, 286
  glycogen metabolism in, 82
  in nervous system, 229
Skin
  autoregulation of, 286
  collagen in, 46
  pigmentation, 52, 80
  vitamin D, 66
  wrinkles of aging, 48
Skin cancer, **454**
  albinism and, 448
  Lynch syndrome and, 371
  sunburn and, 453
Skin (dermatology), 446–456
  blistering disorders, **452**
  common disorders, **449**
  infections, **451**
  layers of, **446**
  microscopic terms, **448**
  morphology, **447**
  vascular tumors, **450**
Skin drug reactions, **241**
Skin flora, 174
Skin infections, 139
Skin lesions
  café-au-lait spots, 53, 399, 495
  hyperextensibility, 47
  inflammatory bowel disease, 365
  kwashiorkor, 67
  scaling, 148
  scaly, 43, 62
  telangiectasias, 303
Skinner’s operant conditioning quadrant, 524
Skin ulcers, 154
Skip lesions, 365, 664
Slapped cheek rash, 179
Sleep
  enuresis during, 342
  ghrelin/leptin production, 317
  GHRH production, 317
Sleep apnea, **642**
  pulse pressure in, 272
  pulsus paradoxus in, 300
Sleep disturbances
  apnea, 642
  menopause as cause, 600
Sleep physiology, **467**
Sleep problems
  benzodiazepines, 467
  benzodiazepines and, 540
  β-blockers, 237
  delirium and, 528
  generalized anxiety disorder, 533
  in geriatric patients, 259
  major depressive disorder, 531
  paroxysmal nocturnal dyspnea, 298
  stimulant withdrawal, 540
  varenicline, 546
Sleep terror disorder, **538**
Sleepwalking, 467, 515
Sliding hiatal hernias, 355
Slipped capital femoral epiphysis, 436
Slow twitch muscle fibers, 433
Small bowel disease, 358

- Small cell lung cancer, **647**, 668
  - carcinogens causing, 219
  - Lambert-Eaton myasthenic syndrome, 445
  - neuromuscular paraneoplastic syndromes and, 217
  - topotecan for, 419
- Small intestine, 356
- Small lymphocytic lymphoma (SLL), 410
- Small nuclear ribonucleoproteins (snRNPs), 39
- Smallpox, 160
- Smoke inhalation, 640
- Smoking
  - abdominal aortic aneurysms and, 292
  - atherosclerosis and, 292
  - Buerger disease and, 302, 661
  - bupropion for cessation, 546
  - carcinogenecity of, 219
  - cataracts, 505
  - cervical cancer and, 609
  - colorectal cancer and, 371
  - emphysema, 638, 655
  - esophageal cancer and, 361
  - head and neck cancer, 636
  - hormonal contraception, 622
  - Legionnaires' disease, 139
  - lung cancer, 647
  - pancreatic cancer and, 380
  - placental abruption and, 606
  - renal cell carcinoma, 568
  - renal tumors, 668
  - saccular aneurysms, 486
  - squamous cell carcinoma of bladder, 569
  - stomach cancer and, 362
  - teratogenic effects, 582
  - transitional cell carcinoma, 569
  - varenicline for cessation, 546
- Smooth endoplasmic reticulum, **42**
- Smooth muscle
  - autoantibody to, 111
  - contraction of, **434**
  - glomus tumors, 450
  - nervous system and, 229
  - respiratory tree, 628
  - tumor nomenclature in, 216
- Smudge cells, 410
- SNRIs (serotonin-norepinephrine reuptake inhibitors), **545**
  - cliinical use, 542
  - generalized anxiety disorder, 533
  - major depressive disorder, 531
  - mechanism of, 544
  - serotonin syndrome, 545
- Snuffles, 143
- Soap bubble on X-ray, 660
- Social anxiety disorder, 533
  - drug therapy for, 542
  - SSRIs for, 545
  - venlafaxine for, 545
- Sodium channel blockers, **308**
- Sodium channels
  - cystic fibrosis, 56
  - epilepsy drug effects, 514
  - glucose and, 314
  - local anesthetic effects, 519
  - pacemaker action potential and, 281
  - permethrin, 196
- Sodium oxybate, 538
- Sodium-potassium channels, 229
- Sodium-potassium pump, **45**
- Sodium stibogluconate, 154, 196
- Sofosbuvir, 200, 661
- Solifenacin, 233
- Solitary functioning kidney, **549**
- Solitary nucleus of medulla, 285
- Somatic hypermutation, 97
- Somatic mosiacism, 53
- Somatic symptom disorder, 536
- Somatosensory cortex, 471
- Somatostatin
  - glucagon and, 315
  - hypothalamic/pituitary drugs, 342
  - hypothalamic-pituitary hormones, 315
  - production of, 313
  - regulatory substances, 356
  - secretory cell locations, 357
- Somatostatinomas, **338**
- Somatotropin. *See* Growth hormone (GH)
- Sonic hedgehog gene, 580
- Sonic hedgehog signaling pathway, 461
- Sorbitol, **77**
- Sorbitol dehydrogenase, 77
- Sotalol, 309
- Southern blot, 49
- Southwestern blot, 49
- Space of Disse, 352
- Spaghetti and meatballs appearance, 148
- Spasticity, 515
- Spastic paralysis
  - *Clostridium tetani*, 134
  - tetanospasmin, 128
- Specificity equation, 247, 669
- Spermatic cord, 354
- Spermatoceles, 618
- Spermatocytes, 594
- Spermatogenesis, 594, **601**
  - cryptorchidism and, 617
  - prolactin effect on, 316
- Spermatogonia, 594
- Sphenomandibular ligament, 587
- Sphenoparietal sinus, 473
- Spherical bacteria, 121
- Spherocytes, 395
  - extravascular hemolysis, 399
- Sphincter of Oddi, 353, 356
- Sphingolipidoses, 84
- Sphingomyelin, 84
- Sphingomyelinase, 84
- Spider angiomas
  - ataxia-telangiectasia, 113
  - cirrhosis, 372
- "Spike and dome" cells, 566
- Spikes on basement membrane, 660
- Spina bifida
  - Dandy-Walker syndrome, 462
  - labs/findings, 657
  - neural tube defect, 461
- Spina bifida cystica, 461
- Spina bifida occulta, 461
- Spinal cord
  - embryologic derivation, 581
  - lesions of, **500**
  - spinal nerves, **478**
  - tracts of, **478**, **479**
- Spinal tap, bloody/yellow, 657
- Spinothalamic tract, 479
- Spiral bacteria, 121
- Spirochetes, **142**
- Spironolactone, 576, 620, 623, 609
  - for heart failure, 298
  - metabolic acidosis, 561
  - for PCOS, 609
- Splay (glucose clearance), 554
- Spleen
  - blood supply and innervation of, 348
  - diagram of, 94
  - embryology, 345
  - in gastrointestinal anatomy, 346
  - ischemia susceptibility, 206
  - thrombocytes in, 386
- Splenectomy, 400
- Splenic artery, 349
- Splenomegaly
  - amyloidosis and, 213
  - anemia, 153
  - cirrhosis, 372
  - hairy cell leukemia, 410
  - hereditary spherocytosis, 400
  - histoplasmosis, 147
  - malaria, 153
  - rheumatoid arthritis, 439
  - visceral leishmaniases, 154
- Splenorenal ligament, 346
- Spliceosome, 39
- Splice site mutations, **36**
- Splicing of pre-mRNA, **39**
- Splinter hemorrhages, 299, 656
- Splitting, 525
  - in borderline personality disorder, 535
- Splitting of heart sounds, **277**
- Spondyloarthropathy, 213
- Spongiosis, 448
- Spontaneous abortion
  - antiphospholipid syndrome, 443
  - fibroid tumors, 612
  - *Listeria monocytogenes*, 135
  - syphilis, 178
  - Vitamin A excess, 582
  - warfarin, 582
- Spontaneous bacterial peritonitis, 373
- Sporadic porphyria cutanea tarda, 169
- Spore-forming bacteria, **127**
- Spores, 120
- *Sporothrix schenckii*, **150**
- Sporotrichosis, 150
- Sprue
  - fat-soluble vitamin deficiencies and, 61
  - vitamin B_{12} deficiency, 65
- Squalene epoxidase, 194, 195
- Squamous cell carcinomas
  - actinic keratoses and, 664
  - anus and cervix, 173
  - bladder, 156, **569**
  - carcinogens causing, 219
  - cervix, 609
  - cytokeratin stain, 44
  - esophagus, 360, 361, 665
  - head and neck, 636
  - hypercalcemia and, 217
  - lungs, 647
  - pectinate line and, 351
  - penis, 617
  - of skin, 454
  - sunburn and, 453
- Squamous epithelium, 628
- *SRY* gene, **589**
- SSRIs (selective serotonin reuptake inhibitors), **545**
  - adjustment disorder, 533
  - anxiety disorders, 532
  - atypical depression, 531
  - binge eating disorder, 537
  - clinical use, 542
  - generalized anxiety disorder, 533
  - major depressive disorder, 531
  - mechanism of, 544
  - obsessive-compulsive disorder, 533
  - panic disorder, 533
  - phobias, 533
  - postpartum depression, 532
  - PTSD, 534
  - sexual dysfunction from, 537
- Stable angina, 293
- Stable cells, 42
- Stab wounds and winged scapula, 428
- Staghorn calculi, 567
- Stains (bacterial), **122**
- Standard deviation, 251
- Standard error of the mean, 251
- Stapedial artery, 586
- Stapedius muscle, 587
- Stapes (middle ear), 503
- Stapes (ossicles), 587
- Staphylococcal scalded skin syndrome, 451
- *Staphylococcus* spp
  - antibiotic tests for, 130
  - catalase-positive organism, 124
  - Chédiak-Higashi syndrome, 113
  - Gram-positive algorithm, 130
  - taxonomy, 121
- *Staphylococcus aureus*, **131**
  - bacterial endocarditis, 299
  - β-hemolytic nature of, 131
  - brain abscesses, 176
  - cephalosporins, 185
  - cystic fibrosis, 56, 175
  - dapsone, 191
  - exotoxin production, 129
  - food poisoning, 174
  - immunocompromised patients, 175
  - influenza, 165
  - IV drug use, 175
  - lung abscesses, 646

  nosocomial infection, 175, 181
  osteomyelitis and, 176
  penicillins for, 184
  pigment production, 125
  pneumonia, 645
  postviral infection, 175
  prophylaxis for, 194
  septic arthritis, 441
  skin infections, 451
  T cell effects of, 106
Staphylococcus epidermidis, **131**
  bacterial endocarditis, 299
  Gram-positive testing, 130
  in vivo biofilm production, 125
  normal flora, 174
  nosocomial infection, 181
  osteomyelitis, 176
  urease-positive, 124
  vancomycin for, 186
Staphylococcus gallolyticus, 133
Staphylococcus pneumoniae, 636
Staphylococcus saprophyticus, **132**
  Gram-positive testing, 130
  kidney stones, 567
  urinary tract infections, 570, 668
  UTIs, 177
Starling curve, **274**
Starling forces, 287
"Starry sky" appearance of B cells, 408
Start and stop codons, **37**
Starvation, 87
Statins
  for acute coronary syndromes, 296
  hepatitis, 240
  myopathy, 241
Statistical distribution, **251**
Statistical hypotheses, **251**, **252**, 253
Statistical tests, **253**
Status epilepticus, 487
  treatment, 514, 515
Stavudine, 197, 199
Steady state, 225
Steatohepatitis, 372
Steatorrhea
  cystic fibrosis, 56
  malabsorption syndromes as cause, 364
  octreotide as cause, 382
  orlistat as cause, 383
  somatostatinomas, 338
Steeple sign (X-ray), 166, 660
Stellate cells, 352
Stellate infiltration of ductal carcinoma, 616
Stem cells in aplastic anemia, 399
Stercobilin, 359
Steroid hormone signaling pathways, **322**
Steroids
  acute pancreatitis, 380
  berylliosis, 641
  lupus, 443
  multiple sclerosis, 493
  osteoporosis and, 435
  polymyositis/dermatomyositis, 445
  sarcoidosis, 444
Steroids (exogeneus)
  adrenal insufficiency, 324
  CRH levels in, 315
Steroid synthesis, 68
Stevens-Johnson syndrome, 190, 452, 514
  as drug reaction, 241
  sulfa drug allergies, 243
Stimulant laxatives, 383
Stimulants for ADHD, 527
St. John's wort, 243
St. Louis encephalitis, 163
Stomach
  cholecystokinin effect on, 356
  in gastrointestinal anatomy, 346
  histology of, 347
  sclerosis of, 446
  secretin effect on, 356
"Stone" bone appearance, 435
Straight sinus, 473
Stranger anxiety in infants, 258
Strategies
  clinical vignette, 21
  test-taking, 20–21
Strawberry cervix, 154, 177, 180
Strawberry hemangiomas, 450, 668
Strawberry tongue
  causes of, 656
  Kawasaki, 302
  scarlet fever, 132
Streak ovaries, 656
Streptococcus spp
  antibiotic tests for, 130
  Chédiak-Higashi syndrome, 113
  Gram-positive algorithm, 130
  septic arthritis, 441
  taxonomy, 121
Streptococcus agalactiae (Group B strep), **133**
  β-hemolytic nature of, 131
  encapsulated bacteria, 124
  Gram-positive testing, 130
  immunodeficient patients, 114
  meningitis, 176
  in neonates, 178
  pneumonia, 175
  prophylaxis for, 194
  splenic dysfunction, 94
Streptococcus bovis, **133**
  bacterial endocarditis, 299
  colon cancer, 660
  colorectal cancer and, 371
Streptococcus mitis, 132
Streptococcus mutans
  biofilm production, 125
  dental caries, 132
  normal flora, 174
Streptococcus pneumoniae, **132**
  α-hemolysis, 131
  bacterial meningitis, 664
  chloramphenicol, 188
  cystic fibrosis, 175
  encapsulated bacteria, 124
  Gram-positive testing, 130
  IgA protease and, 125
  immunodeficient patients, 114
  influenza, 165
  IV drug use and, 175
  meningitis, 176
  penicillin G/V for, 183
  pneumonia, 175, 645
  postviral infection, 175
  splenic dysfunction, 94
  transformation in, 126
Streptococcus pyogenes (Group A strep), **132**
  acute poststreptococcal glomerulonephritis, 564
  bacitracin response, 657
  β-hemolysis, 131
  clindamycin, 188
  exotoxin produced by, 129
  Gram-positive testing, 130
  M protein and, 125
  penicillin G/V for, 183
  rash, 179
  skin infections, 451
  T cell effects of, 106
Streptococcus sanguinis, 125
Streptogramins, 194
Streptokinase, 391, 415
Streptolysin O, 129
Streptomycin, 183, 187, **193**
Streptozocin, 418
Streptrogramins, 183
Stress incontinence, 569
Striated muscle, 216
Striatum, 470, 484
"String sign" (X-ray), 365
Stroke, **484**
  ADP receptor inhibitors for, 415
  atrial fibrillation and, 284
  central post-stroke pain syndrome, 485
  cilostazol/dipyridamole for, 415
  direct factor Xa inhibitors for, 415
  eclampsia, 608
  homocystinuria, 80
  hypertension, 290
  hypertensive emergency and, 290
  sickle cell anemia, 400
  syphilis, 143
  thrombolytics for, 415
  vertigo, 503
  warfarin for, 414
Stroke volume, 273, 669
Strongyloides spp, 154
Strongyloides stercoralis, 155
ST segment, 282
ST-segment elevation MI (STEMI)
  diagnosis of, 293, **295**
  treatments for, 296
Studies
  error types, 246
Studying for USMLE Step 1 exam
  materials for, 18–19
  in preclinical years, 13–14
  timeline for, 14–17
Study materials, 18–19
Study schedule, 14–18
Sturge-Weber syndrome, 495, 656
Stylohyoid ligament, 587
Stylohyoid muscle, 587
Styloid process, 587
Stylopharyngeus, 587
Subacute cerebellar degeneration, 647
Subacute combined degeneration, 65
Subacute endocarditis
  enterococci, 133
  Staphylococcus gallolyticus, 133
Subacute granulomatous thyroiditis, 328
Subacute sclerosing panencephalitis (SSPE), 166
Subacute thyroiditis, 211
Subarachnoid hemorrhage, 483, 488
  labs/findings, 657, 661
  nimodipine for, 304
  presentation, 656
Subarachnoid space, 478
Subclavian arteries, 473, 586
Subcutaneous fat
  erythema nodosum in, 453
  skin layers, 446
Subcutaneous nodules, 132
Subcutis, 446
Subdural hematomas, 483
  child abuse sign, 526
Subendocardium, 206
Sublimation, 525
Submucosa, 347
Submucosal gland, 347
Submucosal polyps, 370
Subscapularis muscle, 425
Substance abuse
  adult T-cell lymphoma and, 408
  Candida albicans, 149
  delirium with, 528
  dementia, 529
  dissociative identity disorder and, 528
  loss of orientation with, 528
  parental consent, 254
  Pseudomonas aeruginosa, 139
  stages of change in overcoming, **539**
  suicide and, 532
  torsades de pointes in, 283
  tricuspid valve endocarditis and, 299
Substance P, 520
Substance P antagonist, 383
Substance use disorder, **538**
Substantia nigra
  Parkinson disease, 655
Substantia nigra pars compacta, 470
Subthalamic nucleus, 470
  lesions in, 481
Subunit vaccines, 158
Succimer
  heavy metal toxicity, 239
  lead poisoning, 397
Succinate dehydrogenase, 63
Succinylcholine, 520
Succinyl-CoA
  gluconeogenesis, 74
  TCA cycle, 73
Sucking reflex, 480
Sucralfate, **382**
Sudan stain, 364

Sudden cardiac death, 293
  cocaine use, 540
Sudden death
  cor pulmonale, 643
  pulmonary embolism, 637
  sleep apnea, 642
Sudden infant death syndome (SIDS), 599
Suicidal patients, 256
  confidentiality exceptions and, 255
  elderly, 259
Suicide
  bipolar disorder and, 531
  borderline personality disorder and, 535
  deaths from, **260**
  major depressive disorder and, 531
  physician-assisted, **256**
  risk factors for, **532**
  schizophrenia and, 530
Sulbactam, 184
Sulfadiazine, 190
  mechanism, 183
  Toxoplasma gondii, 152, 663
Sulfa drugs, **243**
  acute pancreatitis, 380
  erythema multiforme, 452
  G6PD deficiency from, 400
  lupus-like syndrome, 241
  megaloblastic, **241**
  rash, 241
Sulfamethoxazole, 183, 190
Sulfapyridine, 382
Sulfasalazine, 243, **382**, 439
Sulfatides, 136, 494
Sulfisoxazole, 183, 190
Sulfonamides, **190**
  acute interstitial nephritis, 572
  cytochrome P-450 and, 243
  hemolysis in G6PD deficiency, 241
  hypothyroidism, 240
  mechanism, 183
  Nocardia spp, 135
  photosensitivity, 241
  pregnancy contraindication, 201
  trimethroprim, 190
  vitamin B_9 deficiency, 64
Sulfonylureas, 340
  disulfiram-like reaction, 242
  insulin and, 314
Sulfur granules, 125, 135
Sumatriptan, 516
  cluster headaches, 488
  coronary vasospasm, 239
Sunburn, 453
Superficial inguinal lymph nodes, 93
Superficial inguinal nodes, 591
Superficial inguinal ring, 354
Superior cerebellar artery, 473
Superior colliculi, 475
Superior gluteal nerve, 431
Superior mesenteric artery, 348
Superior mesenteric artery (SMA) syndrome, 348
Superior mesenteric lymph nodes, 93
Superior mesenteric vein, 350
Superior oblique muscle, 510
Superior ophthalmic vein, 473
Superior orbital fissure, 476
Superior rectal artery, 351
Superior rectal vein, 350
Superior rectus muscle, 510
Superior sagittal sinus, 473
Superior sulcus tumors, 646
Superior vena cava
  embryological development of, 268
  in fetal circulation, 270
Superior vena cava syndrome, **646**
  lung cancer, 647
  Pancoast tumor, 646
Superoxide dismutase, 105
  free radical elimination by, 210
Suppression, 525
Suprachiasmatic nucleus, 466
  sleep physiology and, 467
Suprarenal arteries, 348
Suprascapular nerve, 425
Supraspinatus muscle, 425, 428
Supratentorial mass, 499
Supraventricular tachycardia
  adenosine for diagnosing, 310
  β-blockers for, 237, 309
  calcium channel blockers for, 310
Suramin, 196
Surface F protein, 165
Surfactant, 631
Surgical neck of humerus, 432
Surgical procedures
  readmissions with, 261
Surrogate decision-maker, 255
Swan-Ganz catheter, 286
Swarming, 177
Sweat glands
  embryologic derivation, 581
  nervous system and, 229
  pilocarpine effects, 232
Swiss cheese model, **262**
Sydenham chorea, 132, 300
Sylvian fissure, 471
Sympathetic nervous system, 229
  male sexual response, 593
Sympathetic receptors, 230
Sympatholytic drugs, **235**
Sympathomimetic drugs, **234**
Symphysis pubis, 593
Symptom duration, 534
Syncope
  during exercise, 297
  pulsus parvus et tardus, 279
Synctiotrophoblasts
  β-hCG and, 220
Syncytiotrophoblasts, 584, 598
  choriocarcinomas and, 605
  hCG secretion by, 598
Syndrome of apparent mineralocorticoid excess (SAME), 556
Syndrome of inappropriate antidiuretic hormone secretion. *See* SIADH
Synergistic drug interactions, 225
Syngeneic grafts, 114
Syphilis, **143**
  as granulomatous disease, 211
  presentation, 655, 656
  prophylaxis for, 194
  STI, 180
  tabes dorsalis, 500
  testing for, 143
  thoracic aortic aneurysms and, 292
  ToRCHeS infection, 178
Syphilitic heart disease, **300**
Syringomyelia, **462**
  Horner syndrome, 509
  spinal cord lesions, 500
Systemic mycoses, **147**
Systemic primary carnitine deficiency, 85
Systole
  cardiac cycle, 276
  heart murmurs of, 278, 279
  heart sounds of, 278
Systolic ejection, 276
Systolic murmur, 297
Systolic pressure, 272

T

Tabes dorsalis
  spinal cord lesions, 500
  syphilis, 143, 180
Tachyarrhythmia
  isoproterenol for evaluating, 234
  thyroid storm, 329
Tachycardia
  alcohol withdrawal, 541
  amphetamines, 540
  cause and prevention, 304, 305
  delirium tremens, 542
  MDMA as cause, 541
  metronidazole, 191
  PCP, 541
  phenoxybenzamine, 236
  pulmonary embolism, 637
  stimulants and, 540
  thyroid hormones, 342
  tricyclic antidepressants, 545
  Wolff-Parkinson-White syndrome, 283
Tachyphylactic drug interactions, 225
Tachypnea
  asthma, 638
  pulmonary embolism, 637
Tacrine, 518
Tacrolimus
  hyperglycemia, 240
  immunosuppression, 116
  targets of, 117
Tactile hallucinations, 529
  cocaine, 540
Tadalafil, 623
Taenia solium, 156, 157
Takayasu arteritis, 211, **302**
Talcosis, 211
Tamoxifen, **421**, 621
  for breast cancer, 662
  hot flashes, 240
Tamsulosin, 236, 619, **623**
Tanner stages (sexual development), **602**
Tarasoff decision, 255
Tardive dyskinesia
  as drug reaction, 242
  metoclopramide adverse effect, 383
  nigrostriatal pathway, 468
Target cells, 94, 395
Tarsal tunnel syndrome, 430
TATA box, 38
Tau proteins, 660
Taxonomy (bacterial), **121**
Tay-Sachs disease
  frameshift mutation, 36
  lysosomal storage disease, 84
  presentation, 652
Tazobactam, 184
TBG. *See* Thyroid-binding globulin
TCA cycle, **73**
  diagram, 70
  hyperammonemia, 78
  metabolic site, 68
  pyruvate metabolism, 73
  rate-determining enzyme for, 69
T cells, **388**
  activation, **99**
  adaptive immunity, 95
  anergy, 106
  cell surface proteins, 106
  corticosteroid effects, 116
  cytokine secretion, 104
  cytotoxic, 98
  differentiation of, **97**
  disorders of, 112, 113
  functions, 97
  helper, 98
  leflunomide effects, 456
  lymph nodes, 92
  major functions of, 97
  neoplasms, 408
  regulatory, 98
  sirolimus effect, 116
  spleen, 94
  thymus, 94
  untreated HIV, 172
Tearing stimulation, 232
Teenagers
  common causes of death, 260
Teeth
  congenital syphilis, 143
  demeclocycline and, 342
  dental caries, 132
  dentinogenesis imperfecta, 47
  discoloration, 188, 201, 241, 582
  enamel erosion (bulimia nervosa), 537
  Gardner syndrome, 370
  osteogenesis imperfecta, 47
  retained primary, 112
  Sjögren syndrome and, 441
Telangiectasias
  ataxia-telangiectasia, 37
  autosomal dominant disease, 303
  basal cell carcinomas, 454
  CREST syndrome, 446
  Osler-Weber-Rendu syndrome, 656

Telencephalon, 460
Tellurite agar, 123
Telomerase, **35**
Telophase, 42
Temazepam, 515
Temperature receptors, 464
Temperature regulation, 466
Temporal arteritis
    associations, 668
    ESR in, 212
    as granulomatous disease, 211
    polymyalgia rheumatica, 444
Temporalis muscle, 587
Temporal lobe, 471, 484
Temporal lobe encephalitis, 160
Tendinopathy (rotator cuff), 425
Tendinous xanthomas, 291
    familial hypercholesterolemia, 90
Tendonitis
    as drug reaction, 241
    fluoroquinolones, 191
Tendons
    collagen in, 46
Tenecteplase, 391, 415
Teniposide, **419**
    in cell cycle, 416
Tennis elbow, 426
Tenofovir
    Fanconi syndrome, 556
    HIV therapy, 199
    mechanism (diagram), 197
Tenosynovitis, 441
Tension headaches, 488
Tension pneumothorax, 643, 644
Tensor fascia latae muscle, 431
Tensor tympani muscle, 587
Tensor veli palatini muscle, 587
Tentorium cerebelli, 499
Teratogens, **582**
    ACE inhibitors as, 577
    aminoglycosides, 187
    angiotensin II receptor blockers as, 577
    carbamazepine as, 514
    griseofulvin, 196, 201
    leflunomide, 456
    lithium as, 544
    methimazole as, 341
    PTU in pregnancy, 341
    ribavirin, 200, 201
    vitamin A, 62
    warfarin as, 414
Teratomas, 618
Terazosin, 236, 619
Terbinafine, 194, **195**
Terbutaline, **622**
Teres minor, 425
Teriparatide, 435, **457**
Terminal bronchioles, 626
Terminal deoxynucleotidyl transferase (TdT), 100
Termination of protein synthesis, 41
Tertiary adrenal insufficiency, 324
Tertiary hyperparathyroidism, 332
Tertiary syphilis
    aortic aneurysms, 664
    as granulomatous disease, 211
    presentation, 655, 656
Tesamorelin, 315
Testes, 593
    descent of, **591**
    embryologic derivation, 581
    lymphatic drainage of, 591
    progesterone production, 595
Testicular atrophy
    alcoholism, 541
    cirrhosis, 372
    muscular dystrophy, 57
Testicular cancer
    bleomycin for, 418
    cisplatin/carboplatin for, 419
Testicular/ovarian arteries, 348
Testicular tumors, **618**
    germ cell, 619
    non-germ cell, 619
Testing agencies, 22
Testis-determining factor, 589
Testosterone, 600, **623**
    androgen insensitivity syndrome, 604
    cryptorchidism, 617
    Klinefelter syndrome, 603
    Leydig cell secretion, 594
    pharmacologic control, 620
    Sertoli cells, 594
    SHBG effect on, 322
    signaling pathways for, 322
    spermatogenesis, 594
Testosterone-secreting tumors, 604
Testosterone synthesis, 195
Test-taking strategy, 20–21
Tetanospasmin, 128, 134
Tetanus
    exotoxins, 127
    spore-forming bacteria, 127
    vaccine, 134
Tetanus toxin, 107, 134
Tetany
    hypocalcemia, 560
    hypocalcemic, 66
    hypoparathyroidism, 331
    thymic aplasia, 112
Tetrabenazine
    for Huntington disease, 518
    Tourette syndrome, 527, 542
Tetracaine, 519
Tetracyclines, **188**
    esophagitis, 240
    Fanconi syndrome, 242, 556
    mechanism (diagram), 183
    photosensitivity, 241
    protein synthesis inhibition, 187
    pseudotumor cerebri and, 491
    teratogenicity, 201, 582
    tooth discoloration, 241
Tetrahydrofolic acid, 64, 190
Tetralogy of Fallot, **288**
    22q11 syndromes, 290
    cyanosis caused by, 665
    fetal alcohol syndrome, 290
    lab findings in, 657
    outflow tract formation, 269
    thymic aplasia, 112
Tetrodotoxin, 238
TGF-β
    regulatory T cells, 98
    in wound healing, 211
Thalamus, 460, **468**
    neuropathic pain, 485
Thalassemia, 396
    in anemia taxonomy, 396
    target cells in, 395
Thalidomide, 582
Thayer-Martin agar, 122, 123
Theca interna cells, 595
Theca-lutein cysts, 605, 610
Thecomas, 610
Thenar muscles, 428, 429
Theophylline, 649
    cytochrome P-450 and, 243
    therapeutic index value of, 228
Therapeutic antibodies, **118**
Therapeutic index, **228**
Therapeutic privilege, 254
Thermogenin, 74
Thiazide diuretics
    heart failure, 298
    hypertension, 304
Thiazides, **576**
    gout, 241
    site of action, 574
Thiazolidinediones, 340
Thick ascending loop of Henle
    Bartter syndrome and, 556
    ethacrynic acid effect on, 575
    loop diuretics effect on, 575
    nephron physiology, 555
Thin descending loop of Henle, 555
Thionamides, **341**
Thiopental, 515, 519
Thioridazine, 543
Thirst
    hypothalamus and, 466
    renin-angiotensin-aldosterone system and, 558
30S inhibitors, 187
Thoracentesis, 644
Thoracic aortic aneurysm, 290, 292
Thoracic duct, 93
Thoracic outlet syndrome, 428
Threadworms, 155
Threonine, 77
Threonine kinase, 218
Thrombi
    atherosclerosis, 292
    mural, 296
    post-MI, 294
Thrombin, 413
Thrombocytes
    liver markers, 373
    in wound healing, 211
Thrombocytes (platelets), **386**
    aggregation inhibition, 415
    chronic myeloproliferative disorders, **411**
    disorders, **405**
    heparin adverse effects, 413
    leukemias, 410
    mixed coagulation disorders, **406**
    platelet plug formation, 393
    thrombolytics and, 415
    transfusion of, 399, 407
Thrombocytopenia, 386
    blood transfusion therapy for, 407
    cirrhosis, 372
    Class IA antiarrhythmics, 308
    cytarabine, 417
    as drug reaction, 241
    Escherichia coli, 140
    ganciclovir, 198
    glycoprotein IIb/IIa inhibitors as cause, 415
    heparin adverse effects, 413
    immunosuppressants, 116
    oxazolidinones, 189
    protease inhibitors, 199
    recombinant cytokines, 117
    sulfa drug allergies, 243
    ToRCHeS infections, 178
    Wiskott-Aldrich syndrome, 113
Thrombocytosis, 94
Thromboembolic event
    atrial fibrillation, 284
Thrombogenesis, **393**
Thrombolytic drugs, 391, **415**
Thrombomodulin
    in thrombogenesis, 393
Thrombophlebitis
    pancreatic cancer, 380
    vancomycin, 186
Thrombopoietin receptor agonists, 117
Thrombopoietin signaling pathways, 322
Thrombosis
    celecoxib, 456
    essential thrombocythemia, 411
    homocystinuria, 80
Thrombotic complications, 241
Thrombotic endocarditis, 665
Thrombotic stroke, 482
Thrombotic thrombocytopenic purpura (TTP), 395, **405**
Thromboxane, 455
Thrush
    Candida albicans, 149
    hairy leukoplakia vs, 451
    HIV-positive adults, 173
    nystatin, 195
    SCID, 113
Thumbprint sign (X-ray), 138
Thumb sign (X-ray), 660
Thymic aplasia, 112, 588
    chromosome association, 60
    hypoparathyroidism, 331
    lymphopenia with, 402
    22q11 deletion syndromes, 61
Thymic cortex
    T cell selection in, 97
Thymic hyperplasia, 445
Thymic shadow, 113
Thymidine, 190
Thymidine kinase, 197
Thymidylate, 33
Thymomas
    Good syndrome and, 217
    myasthenia gravis, 217, 445

- Thymus, **94**
  - benign neoplasm, 94
  - fetal development, 312
  - T cell differentiation, 97
  - T cell origination in, 388
- Thymus-dependent antigens, 101
- Thymus-independent antigens, 101
- Thyroglobulin
  - function of, 321
- Thyroglobulin autoantibodies, 111
- Thyroglossal duct cyst, 312
- Thyroid adenomas, 327, **330**
- Thyroid cancer, **330**
  - associations, 668
  - carcinogens causing, 219
  - goiter, 327
  - metastases of, 221
  - Psammoma bodies in, 220
- Thyroid cartilage, 587
- Thyroid cysts, 327
- Thyroid development, 312
- Thyroidectomy, 330
- Thyroid hormones, **321**
  - signaling pathways for, 322
  - in toxic multinodular goiter, 329
- Thyroiditis, 211
- Thyroidization of kidney, 570
- Thyroid lymphomas, 330
- Thyroid peroxidase
  - thionamide effect on, 341
  - thyroid hormones and, 321
- Thyroid-regulating hormone (TRH)
  - signaling pathways for, 322
  - thyroid hormones and, 321
- Thyroid replacement therapy, 435
- Thyroid-stimulating hormone
  - Graves disease and, 329
  - hyperthyroidism, 327
  - hypothyroidism, 327
  - secretion of, 313
  - signaling pathways of, 322
- Thyroid storm, 329
- Thyrotropin-releasing hormone (TRH), 315, 316
- Thyroxine, 335
- Thyroxine-binding globulin (TBG), 321
- Tiagabine, 514
- TIBC
  - anemia of chronic disease, 399
  - lab values in anemia, 402
- Tibial nerve, 430
- Ticagrelor, 415
- Ticarcillin, 183
  - characteristics of, 184
  - *Pseudomonas aeruginosa*, 139
- Ticks (disease vectors), 144, 145, 153
- Ticlopidine, 393, 415
- Tics (Tourette syndrome), 527
- Tidal volume (TV), 630
- Tigecycline, 188, 194
- Tight junctions, 447, 466
- Timolol, 237, 309, 521
- Tinea, **148**, 196
- Tinea capitis, 148
- Tinea corporis, 148
- Tinea cruris, 148
- Tinea pedis, 148
- Tinea unguium, 148
- Tinea versicolor, **148**
- Tinel sign, 427
- Tinnitus
  - streptomycin, 193
- Tiotropium, 233
- Tirofiban, 393, 415
- Tissue factor activation, 129
- Tissue factor pathway, 391
- Tissue plasminogen activator (tPA)
  - for ischemic stroke, 482
- TMP-SMX, 190
  - hyperkalemic renal tubular acidosis, 562
  - for *Pneumocystis jirovecii*, 150
  - prophylaxis, 194
  - UTI prophylaxis, 664
- TNF-α, 104
  - endotoxins and, 129
  - extrinsic pathway and, 204
  - in granulomatous diseases, 211
  - Graves disease and, 329
- TNF-α inhibitors, 439, **457**
- TNF (tumor necrosis factor), 221
- TNM tumor staging, 216
- Tobramycin, 183, 187
- Togaviruses
  - characteristics of, 163
  - genomes of, 159
  - rubella as, 165
- Tolbutamide, 340
- Tolcapone, 517
- Toll-like receptors (TLRs), 95
- Tolterodine, 233
- Tolvaptan, 334, 342
- Tongue development, **463**
- Tonic-clonic seizures, 487
  - drug therapy for, 514
  - treatment, 663
- Tonic seizures, 487
- Tonsils
  - agammaglobulinemia, 112
  - immune system organ, 92
- Tophi in gout, 656
- Topiramate
  - epilepsy, 514
  - migraine headaches, 488
  - pseudotumor cerebri, 491
- Topoisomerase inhibitors, 416
- Topoisomerases, 191
- Topotecan, 416, **419**
- ToRCHeS infections, 165, **178**
  - cataracts, 505
- Torsades de pointes, **283**
  - Class IA antiarrhythmics, 308
  - as drug reaction, 239
  - hypomagnesemia, 560
  - ibutilide, 309
  - magnesium for, 310
  - sotalol, 309
- Torsemide, **575**
- Torus fracture, 424
- Total anomalous pulmonary venous return (TAPVR), 288
- Total lung capacity (TLC), 630
  - flow volume loops, 637
- Total parenteral nutrition (TPN), 379
- Total peripheral resistance, 272, 275
- Tourette syndrome, 527
  - antipsychotics for, 543
  - atypical antipsychotics for, 543
  - drug therapy for, 542
  - obsessive-compulsive disorder and, 533
  - sympatholytic drugs for, 235
- Toxic dose, 228
- Toxic epidermal necrolysis, 452
- Toxicities, **239**
- Toxic multinodular goiter, 329
- Toxic shock-like syndrome, 132
- Toxic shock syndrome, 129
  - exotoxin A, 129
  - presentation, 131
  - *Staphylococcus aureus*, 131
- Toxic shock syndrome toxin, 129
- *Toxocara* spp, 154
- *Toxocara canis*, 155
- *Toxoplasma* spp, 176
- *Toxoplasma gondii*, **152**
  - HIV-positive adults, 173
  - labs/findings, 660
  - ToRCHeS infection, 178
  - treatment, 663
- Toxoplasmosis, 152
  - PCL vs, 408
  - prophylaxis, 190, 194
  - pyrimethamine, 196
- *TP53* gene, 218
- Trabecula
  - lymph node, 92
  - spleen, 94
- Trabecular outflow, 505
- Trachea
  - bifurcation of, 629
  - fetal development, 312
  - respiratory tree, 628
- Tracheoesophageal anomalies, **344**
- Tracheoesophageal fistula, 344
- Tramadol, **521**
  - seizures, 242
- Transcortical aphasia, 486
- Transcription factor, 218
- Transduction, 126
- Transference, **524**
- Transferrin
  - acute-phase reactant, 102
  - free radical elimination by, 210
  - lab values in anemia, 402
- Transformation, 126
- Transfusion reaction, 108
- Transient arthritis, 142
- Transient ischemic attacks (TIAs), 415, **482**
- Transitional cell carcinomas, 219, **569**
- Transition metals and free radical injuries, 210
- Transition (mutation), 36
- Transjugular intrahepatic portosystemic shunt (TIPS), 350
- Transketolase
  - metabolic pathways, 70
  - vitamin B_1 and, 62
- Transpeptidases, 183
- Transplants
  - immunosuppressants in, 116
  - rejection, **115**
- Transposition, 127
- Transposition of great vessels, **288**
  - cyanosis with, 665
  - embryologic development, 269
  - maternal diabetes ande, 290
- Transsexualism, 537
- Transtentorial herniation, 499
- Transthyretin gene, 213
- Transudate pleural effusion, 644
- Transudate vs exudate, **212**
- Transversalis fascia, 345, 354
- Transverse sinus, 473
- Transversion (mutation), 36
- Transversus abdominis muscle, 354
- Transvestism, 537
- Tr antigens, 217
- Tranylcypromine, 546
- Trapezium bone, 426
- Trapezoid bone, 426
- TRAP stain, 410
- Trastuzumab, 118, **421**
  - toxicities of, 422
- Trastuzumab (Herceptin), 421
- Trauma
  - DIC and, 665
  - pneumothorax, 644
- Traumatic aortic rupture, **292**
- Traumatic pneumothorax, 644
- Travelers' diarrhea, 140
- Trazodone, 546
  - mechanism of, 544
  - priapism, 617
- Treacher Collins syndrome, 587
- Trematodes, **156**
- Tremor
  - immunosuppressants, 116
  - resting, 489, 655
- Trench fever, 157
- Trendelenburg sign, 431
- *Treponema* spp, 142
- *Treponema pallidum*
  - granulomatous diseases caused by, 211
  - penicillin G/V for, 183
  - STI, 180
  - syphilis, 143
  - treatment, 664
- TRH. *See* Thyrotropin-releasing hormone
- Triamcinolone, 455
- Triamterene, 555, 576
- Triazolam, 515
- *Trichinella* spp, 154
- *Trichinella spiralis*, 155, 157
- Trichinosis, 155
- *Trichomonas* spp
  - vaginitis, 177
- *Trichomonas vaginalis*, **154**, 180
- Trichomoniasis, 180
- *Trichophyton* spp, 148

Tricuspid atresia, 269, 288
Tricuspid insufficiency, 276
Tricuspid regurgitation
  carcinoid syndrome as cause, 338
  Ebstein anomaly and, 288
  heart murmurs with, 279
  pansystolic murmur in, 278
Tricuspid stenosis, 278
Tricuspid valve endocarditis, 299
Tricyclic antidepressants (TCAs), **545**
  antimuscarinic reaction, 242
  fibromyalgia, 444
  generalized anxiety disorder, 533
  mechanism of, 544
  naming convention for, 244
  as noradrenergic drug, 231
  serotonin syndrome with, 545
  torsades de pointes, 239
  toxicity treatment for, 239
  as weak bases, 226
Trientine, 378
Trifluoperazine, 543
Trigeminal nerve (CN V), **476**
  brain stem location, 474
  branchial arch derivative, 587
  lesion in, 502
  migraine headaches and, 488
  neuralgia, 488
  pathway for, 476
  tongue, 463
Trigeminal neuralgia, 488
  treatment, 664
Triglycerides
  chylothorax, 644
  dietary, 88
  hepatosteatosis, 68
  hypertriglyceridemia, 90
  insulin and, 314
  Von Gierke disease, 83
Trigone, 550
Triiodothyronine, **342**. *See also* Thyroid hormones
Trimethoprim
  folate deficiency with, 398
  pyrimidine synthesis and, 33
  teratogenicity, 582
Trimethroprim, 183, **190**
Trimming (protein synthesis), 41
Trinucleotide repeat expansion diseases, **58**
Triose kinase, 76
Triple-blinded studies, 246
Triptans, **516**
  angina and, 293
  for migraine headaches, 488
Triquetrum bone, 426
tRNA, **40**
Trochlea, 510
Trochlear nerve (CN IV), **476**
  brain stem location, 474
  cavernous sinus, 512
  ocular motility, 510
  palsy of, 511
  pathway for, 476
Tropheryma whipplei, 122, 364
Tropical sprue, 364
Tropicamide, 233
Troponin C, 433
Troponins, 293, 295
Trousseau sign, 331, 560
Trousseau syndrome
  pancreatic cancer, 380
  as paraneoplastic syndrome, 217
True-negative rate, 247
True-positive rate, 247
Truncal ataxia, 469
Truncus arteriosus
  22q11 syndromes, 290
  cyanosis with, 665
  embryologic development, 268
  thymic aplasia, 112
Trypanosoma brucei, **152**, 196
Trypanosoma cruzi, **154**
  achalasia and, 360
  nifurtimox for, 196
Trypanosome stain, 122
Trypsin, 358
Trypsinogen, 358
Tryptase, 387
Tryptophan, 77, 79
TSC1/TSC2 genes, 218
Tsetse flies (disease vectors), 152
TSH. *See* Thyroid-stimulating hormone (TSH)
TSH receptor autoantibody, 111
t-tests, 253
T-tubule membrane, 433
Tubal ligation, 610
Tuberculoid Hansen disease, 137
Tuberculosis, **136**
  Addison disease, 324
  corticosteroids and, 319
  erythema nodosum, 453
  as granulomatous disease, 211
  isoniazid, 193
  macrophages and, 387
  necrosis and, 205
  silicosis, 641
  $\dot{V}/\dot{Q}$ mismatch, 634
Tuberin protein, 218
Tuberoinfundibular pathway, 468
Tuberous sclerosis, 495
  tumor suppressor genes and, 218
Tubocurarine, 520
Tubular necrosis, 571
Tubulointerstitial inflammation
  WBC casts in, 562
Tularemia, 144
Tumor grade vs stage, 216
Tumor lysis syndrome, 421
  gout, 440
  hyperkalemia, 560
  labs/findings, 660
Tumor markers
  acute lymphoblastic leukemia, 410
  pancreatic adenocarcinomas, 380
  serum, **220**
Tumors
  benign vs malignant, 216
  grade vs stage, **216**
  nomenclature of, **216**
  TNM staging system, 216
Tumor suppressor genes, **218**
Tumor suppressors, 42
Tunica albuginea, 593, 617
Tunica muscularis externa, 347
Tunica serosa, 347
Tunica submucosa, 347
Tunica vaginalis, 591
Turcot syndrome, 370
Turner syndrome, **603**
  cardiac defect association, 290
  coarctation of aorta and, 289
  cystic hygromas, 450
  GH for, 342
  horseshoe kidney, 549
  presentation, 656
T wave, in ECG, 282
21-hydroxylase, 318
21-hydroxylase deficiency, 665
22q11 deletion syndromes, **61**, 290
Twin concordance studies, 246
Twinning, **583**
2-naphthylamine, 219
TXA_2
  aspirin effects, 456
  thrombogenesis, 393
Type 1 muscle fibers, 433
Type 2 muscle fibers, 433
Type I errors in hypothesis testing, **252**
Type I hypersensitivity, 108
  helminths, 154
  IgE antibodies and, 101
Type I hypersensitivity reactions
  mast cells and, 387
Type II errors in hypothesis testing, 252
Type II hypersensitivity, 108
  blood transfusions, 110
  helminths, 154
  organ transplants, 115
Type II hypersensitivity reactions
  rheumatic fever, 300
Type III hypersensitivity, 109
  C3 deficiency and, 103
  organ transplants, 115
Type III hypersensitivity reactions
  acute poststreptococcal glomerulonephritis, 564
Type III secretion system, **125**
Type IV hypersensitivity, 109
  graft-versus-host disease, 115
Type IV hypersensitivity reactions
  contact dermatitis, 449
Typhoid fever, 141
Typhus, **145**
  transmission of, 144, 157
Tyramine, 236
Tyrosinase, 448
Tyrosine
  derivatives of, 79
  as noradrenergic drug, 231
Tyrosine catabolism, **79**
Tyrosine kinase
  endocrine hormone messenger, 322
  glycogen regulation, 81
  insulin and, 314
  as oncogene product, 218
Tyrosinemia, 556
Tyrosine phosphorylation, 314
Tzanck test, 162

U

Ubiquitination, 41
UDP-glucose pyrophosphorylase, 82
UDP-glucuronosyl-transferase, 359
Ulcerative colitis, **365**
  spondyloarthritis, 442
  sulfasalazine for, 382
  treatment, 664
Ulcers
  bismuth/sucralfate for, 382
  complications of, **363**
  Helicobacter pylori, 142
  Zollinger-Ellison syndrome, 338
Ulipristal, 622
Ulnar claw, 427, 429
Ulnar nerve, 426, 427
Ulnar nerve injury, 426
Umbilical artery, 270, 584, 585
Umbilical cord, **585**
Umbilical cord separation delay, 113
Umbilical vein, 584, 585
  blood in, 270
  postnatal derivative of, 270
Umbilicus, 350
UMP synthase, 398
Unambiguous genetic code, **34**
Uncal herniation, 499
Uncinate process, 345
Unconjugated hyperbilirubinemia, 376
Uncoupling agents, 74
Uncus, 499
Undifferentiated thyroid carcinomas, 330
Undulant fever, 144
"Unhappy triad"(knee injuries), 425
Unilateral renal agenesis, **549**
Uniparental disomy, **53**
Universal electron acceptors, **71**
Universal genetic code, **34**
Unnecessary procedure requests, 256–257
Unstable angina, 293, 296
Untreated HIV infection timecourse, **172**
Unvaccinated children, 182
Upper extremity nerves, **427**
Upper motor neuron (UMN) lesions, 502
  Babinski response, 656
Upper respiratory infections (URIs)
  asthma trigger, 638
  rhinosinusitis, 636
Urachal cysts, 585
Urachus, 270, **585**
Uracil, 33
Urea, 79
Urea cycle, **78**
  diagram, 70
  metabolic site, 68
  ornithine transcarbamylase deficiency and, 79
  rate-determining enzyme for, 69

- *Ureaplasma* spp
  - urease-positive, 124
- Urease, 177
- Urease-positive organisms, **124**
- Uremia
  - acute pericarditis, 300
  - ARDS, 642
  - metabolic acidosis, 561
  - renal failure, 571
- Ureter, 550, 589, 592, 593
  - constriction of, 553
  - course of, **550**
  - embryology, 548
  - horseshoe kidney, 549
  - obstruction of, 568
  - transitional cell carcinoma in, 569
  - Y-shaped bifid, 549
- Ureteral orifice, 550
- Ureteric bud, 549
- Ureteropelvic junction obstruction, 549
- Urethra
  - BPH, 619
  - injury to, **593**
- Urethral orifice, 550
- Urethritis
  - chlamydia, 146, 180
  - *Chlamydia trachomatis*, 146
  - gonorrhea, 180
  - reactive arthritis, 442, 656
- Urge incontinence, 569
  - drug therapy for, 233
- Uric acid
  - gout, 457
  - Lesch-Nyhan syndrome, 34
  - Von Gierke disease, 83
- Urinary incontinence, **569**
  - drug therapy for, 233
  - ephedrine for, 234
  - hydrocephalus, 492
  - multiple sclerosis, 493
- Urinary retention
  - atropine, 233
  - bethanechol for, 232
  - delirium, 528
  - neostigmine for, 232
  - tricyclic antidepressants, 545
- Urinary tract infections (UTIs), **177**, **570**
  - antimicrobial prophylaxis for, 194
  - BPH, 619
  - duplex collecting system and, 549
  - enterococci as cause, 133
  - *Klebsiella* as cause, 140
  - organisms causing, **177**
  - *Pseudomonas aeruginosa* and, 139
  - pyelonephritis, 570
  - *Staphylococcus saprophyticus* as cause, 132
  - sulfa drug allergies, 243
  - sulfonamides for, 190
  - TMP-SMX for, 190
- Urine
  - bilirubin and, 359
  - casts in, **562**
  - concentration of, 555
  - diuretic effects on, 576
- Urine pH and drug elimination, **226**
- Urobilin, 359
- Urobilinogen
  - extravascular hemolysis, 399
  - intravascular hemolysis, 399
- Urogenital fold, 590
- Urogenital sinus, 548
- Uroporphyrinogen decarboxylase, 403
- Urosepsis, 570
- Urticaria, 447, 449
  - ethosuximide, 514
  - scombroid poisoning, 238
  - serum sickness, 109
  - sulfa drug allergies, 243
  - as type I hypersensitivity, 108
- USMLE Step 1 exam
  - check-in process, 7
  - clinical vignette strategies, 21
  - content areas covered in, 3
  - failing, 22–23
  - goal-setting for, 12
  - leaving exam early, 7
  - overview of, 2
  - passing rates for, 10
  - practice exams for, 10, 19–20
  - registering for, 5–6
  - rescheduling, 6
  - score notifications for, 7
  - scoring of, 8–9
  - studying for, 13–17
  - testing agencies, 22
  - testing locations, 6
  - test-taking strategies, 20–21
  - time budgeting during, 7–8
  - types of questions on, 8
- Uterine artery, 550, 592
- Uteropelvic junction, 548
- Uterus
  - anomalies of, **590**
  - collagen in, 46
  - epithelial histology, 592
  - genital embryology, 589
  - zygote implantation, 598
- Uterus didelphys, 590
- Uveitis, **506**
  - inflammatory bowel disease, 365
  - sarcoidosis, 444, 652
  - seronegative spondyloarthritis, 442
- Uveoscleral outflow, 505
- U wave in ECG, 282

V

- Vaccination
  - B- and T-cell disorders, 113
  - B-cell disorders, 112
  - splenectomy and, 94
  - thymus-independent antigens, 101
- Vaccines, **107**
  - *Bordetella pertussis*, 139
  - diphtheria, 135
  - encapsulated bacteria, 124
  - *Haemophilus influenzae*, 138, 176
  - live attenuated, 158
  - rabies, 167
  - rotavirus, 164
  - *Salmonella typhi*, 141
  - tetanus, 134
  - viral, 158
- Vagal nuclei, **477**
- Vagina
  - anatomy of, 592
  - drainage of, 591
  - epithelial histology of, 592
  - genital embryology, 589
- Vaginal atrophy
  - hormone replacement therapy, 621
  - menopause, 600
- Vaginal bleeding
  - cervical cancer, 609
  - endometrial disease, 612
  - endometriosis, 613
  - granulosa cell tumors, 611
  - hydatidiform moles, 605
  - thecomas, 610
- Vaginal candidiasis
  - nystatin, 195
- Vaginal clear cell adenocarcinomas, 582
- Vaginal infections, **177**
- Vaginal tumors, **609**
- Vaginismus, 537
- Vaginitis
  - treatment, 661
  - *Trichomonas* spp, 154, 177
  - trichomoniasis, 180
- Vagus nerve (10th cranial nerve)
  - baroreceptors/chemoreceptors and, 285
  - cardiac glycoside effects, 307
  - structures innervated, 357
- Vagus nerve (CN X), **476**
  - brain stem location, 474
  - as branchial arch derivative, 587
  - lesions of, 502
  - pathway for, 476
  - tongue, 463
- Valacyclovir, **197**
- Validity, **249**
- Valine
  - classification of, 77
  - maple syrup urine disease, 80
  - sickle cell disease, 36
- Valproate
  - migraine headaches, 488
  - teratogenicity, 582
  - tonic-clonic seizures, 663
- Valproic acid
  - bipolar disorder, 531, 661
  - epilepsy, 514
  - hepatic necrosis, 240
  - pancreatitis, 240
- Valsalva maneuver, 278
- Valsartan, 577
- Valvular dysfunction, 299
- Vancomycin, **186**
  - *Clostridium difficile*, 134
  - cutaneous flushing, 239
  - functioning of, 183
  - meningitis, 176
  - MRSA, 194
  - toxicity of, 242
- Vanillylmandelic acid (VMA)
  - in neuroblastomas, 325
  - tyrosine catabolism, 79
- Vanishing bile duct syndrome, 115
- Vardenafil, 623
- Varenicline, 540, 546
- Variable expressivity, **52**
- Variance, 251
- Variant angina, 293
- Variceal bleeding, 237
- Varicella zoster virus (VZV), 160, 447, 451
  - guanosine analogs, 197
  - immunodeficient patients, 114
  - meningitis, 176
  - rash, 179
  - Reye syndrome, 373
  - vaccine, 107
- Varices
  - Budd-Chiari syndrome, 375
  - portal-systemic anastomoses, 350
- Varicocelectomy, 618
- Varicoceles, 594, **618**
- Vasa previa, 607
- Vasa vasorum
  - syphilis, 143
- Vascular dementia, 491
- Vascular function curves, **275**
- Vascular inflammation, 207
- Vascular tumors of skin, **450**
- Vasculitides, **302–303**
- Vasculitis
  - intraparenchymal hemorrhage, 483
  - methotrexate for, 417
- Vas deferens, 550, 589, 593
- Vasoactive intestinal polypeptide (VIP), 356
- Vasoconstriction, 558
- Vasoconstrictors, 519
- Vasodilation
  - cilostazol/dipyridamole for, 415
  - sympathetic receptors, 230
- Vasodilators
  - afterload effects, 273
  - aortic dissections, 293
  - atrial natriuretic peptide as, 285
  - coronary steal syndrome, 293
  - nitrates as, 305
- Vasogenic edema, 466
- Vasopressin. *See* Antidiuretic hormone (ADH)
- Vasopressin receptors, 230
- V(D)J recombination, 95
- VDRL false positives, **143**
- Vecuronium, 520
- Veganism and B_{12} deficiency, 398
- VEGF (vascular endothelial growth factor), 211
- Velocardiofacial syndrome, 61
- Vemurafenib, **421**, 454
- Venlafaxine, 545
  - clinical use, 542
  - panic disorder, 533
  - phobias, 533
  - PTSD, 534
- Venodilators, 273

Venous gonadal drainage, 591
Venous return, 275
Venous sinus thrombosis, 473
Venous thromboembolism, 414
Venous thrombosis, 400
  heparin for, 413
  paroxysmal nocturnal hemoglobinuria, 400
Ventilation, **630**
  high altitude, 635
  perfusion and, 634
Ventral lateral (VL) nucleus, 468
Ventral pancreatic bud, 345
Ventral posterolateral (VPL) nucleus, 468
Ventral posteromedial (VPM) nucleus, 468
Ventricles
  embryology, 268
  morphogenesis of, 269
Ventricular aneurysm
  pseudoaneurysm, 296
  true, 294
Ventricular arrhythmia, 294
Ventricular fibrillation
  ECG tracing, 284
  torsades de pointes, 283
Ventricular free wall rupture, 296
Ventricular septal defect (VSD), **289**, 665
  congenital rubella, 290
  cri-du-chat syndrome, 60
  Down syndrome, 290
  fetal alcohol syndrome, 290
  heart murmurs, 279
  outflow tract formation, 269
  pansystolic murmur in, 278
Ventricular system, **474**
Ventriculomegaly, 530
Ventromedial, hypothalamus, 466
Verapamil, 304, 305, 310, 488
Vermal cortex lesions, 469
Verrucae, 449
Vertebrae
  diaphragm, 629
Vertebral artery, 473
Vertebral compression fractures, 435, 668
Vertebral disc herniation, 478
Vertigo, **503**
  Meniere disease as cause, 653
  streptomycin, 193
Vesamicol, 231
Vesicles, 447
Vesicourachal diverticulum, 585
Vesicoureteral reflux, 549
  hydronephrosis, 568
  pyelonephritis, 570
Vesicular trafficking proteins, 43
Vestibular bulbs, 590
Vestibular schwannomas, 496
Vestibulocochlear nerve (CN VIII), **476**
  acoustic neuromas, 464
  brain stem location, 474
  pathway for, 476
VHL gene, 218
  pheochromocytomas and, 326
Vibrio spp, 121
Vibrio cholerae, **141**
  exotoxin production, 128
  Gram-negative algorithm, 137
  watery diarrhea, 175
Vibrio parahaemolyticus, 174
Vibrio vulnificus, 174
Vigabatrin, 514
Vimentin, 44
Vinblastine, 419
  in cell cycle, 416
  microtubules and, 44
Vinca alkaloids, 416
Vincristine, 419
  in cell cycle, 416
  microtubules and, 44
  toxicities of, 422
Vinyl chloride
  angiosarcomas, 375, 450
  as carcinogen, 219
VIPomas
  MEN 1 syndrome, 339
  octreotide for, 382
  regulatory substances, 356
Viral encephalitis, 668
Viral envelopes, **159**
Virchow nodes, 362
Virchow triad, 636
Viridans streptococci, **132**
  α-hemolysis, 131
  bacterial endocarditis, 299
  biofilm production, 125
  brain abscesses, 176
  Gram-positive algorithm, 130
  normal flora, 174
Virilization, 318
Virology, **158–173**
Virulence factors
  bacterial, 125
  Bordetella pertussis, 139
  Escherichia coli, 140
  Salmonella/*Shigella*, 141
  Staphylococcus aureus, 131
Viruses
  diarrhea caused by, 175
  enveloped, 158
  genetics, 158
  immunocompromised patients, 175
  negative-stranded, 164
  pneumonia, 175
  receptors for, 162
  replication of, 159
  segmented, 164
  structure of, 158
  vaccines for, 158
Visceral larva migrans, 155
Visceral leishmaniasis, 154
Viscosity, 274
Vision loss
  glaucoma, 506
  hyperammonemia, 78
  retinal disease, 507–508
Visual cortex, 471, 485
Visual field defects, **511**
Visual hallucinations, 529
Vital capacity (VC), 630
Vitamin A (retinol), 61, **62**
  free radical elimination by, 210
  pseudotumor cerebri, 491
  teratogenicity, 582
Vitamin B_1 deficiency
  brain lesions and, 481
  Korsakoff syndrome, 528
  Wernicke-Korsakoff syndrome, 541
Vitamin B_1 (thiamine)
  functions of, **62**, 70
  maple syrup urine disease, 80
  pyruvate dehydrogenase complex, 72
  solubility of, 61
Vitamin B_2 (riboflavin)
  functions, **63**
  pyruvate dehydrogenase complex and, 72
  solubility of, 61
Vitamin B_3 (niacin)
  derivatives of, 79
  functions, **63**
  lipid-lowering agent, 306
  pyruvate dehydrogenase complex and, 72
  solubility of, 61
  vitamin B_6 and, 63
Vitamin B_5 (pantothenic acid)
  functions, **63**
  pyruvate dehydrogenase complex and, 72
  solubility of, 61
Vitamin B_6 deficiency, 397
  isoniazid, 193
Vitamin B_6 (pyridoxine)
  functions, **63**
  solubility of, 61
Vitamin B_7 (biotin)
  activated carriers, 71
  functions, **64**
  functions of, 69
  pyruvate metabolism, 73, 74
  solubility of, 61
Vitamin B_9 deficiency, 398
  in anemia taxonomy, 396
  neutrophils in, 386
Vitamin B_9 (folate)
  absorption of, 358
  deficiency, 668
  functions, **64**
  solubility of, 61
Vitamin B_{12} (cobalamin)
  absorption of, 358
  functions, **65**
  solubility of, 61
  veganism, 65
Vitamin B_{12} deficiency, 398
  in anemia taxonomy, 396
  dementia caused by, 529
  Diphyllobothrium latum, 156, 157
  neutrophils in, 386
  spinal cord lesions in, 500
Vitamin B_6
  isoniazid, 193
  sideroblastic anemia, 397
Vitamin C (ascorbic acid)
  free radical elimination by, 210
  functions, **65**
  methemoglobinemia, 632
  methemoglobin toxicity, 239
  solubility of, 61
Vitamin D, **319**. *See also* Cholecalciferol
  functions, **66**
  osteoporosis prophylaxis, 435
  PTH and, 320
  signaling pathways for, 322
  solubility of, 61
Vitamin D deficiency, 319, 331
  hyperparathyroidism, 437
  osteomalacia/rickets, 436
Vitamin deficiencies, 668
Vitamin E
  free radical elimination by, 210
  functions, **66**
  solubility of, 61
Vitamin K
  coagulation cascade, 392
  functions, **66**
  solubility of, 61
  warfarin reversal, 664
  for warfarin toxicity, 239, 414
Vitamin K deficiency, 392, 404
  cephalosporins, 185
Vitamin/mineral absorption, **358**
Vitamins, **61–67**
  fat-soluble, **61**
  water-soluble, **61**
Vitelline duct/fistula, **585**
Vitiligo, 448
Vitreous body
  collagen in, 46
Vitreous chamber, 504
VLDL (very low-density lipoprotein), 89
Volume of distribution, 225, 669
Volvulus, **368**
  malrotation, 367
  Meckel diverticulum, 367
vomiting
  GLP-1 analogs, 341
Vomiting
  annular pancreas, 345
  biliary colic, 379
  bilious, 344, 367
  chemotherapy-induced, 383
  diabetic ketoacidosis, 337
  Ebola virus, 167
  food poisoning, 134
  fructose intolerance, 76
  glycylcyclines, 188
  Histoplasma capsulatum, 173
  hyperammonemia, 78
  iron poisoning, 404
  Legionella spp, 181
  Mallory-Weiss syndrome, 360
  maple syrup urine disease, 80
  metabolic alkalosis from, 561
  metoclopramide for, 383
  MI and, 294
  ondansetron for, 383
  posttussive, 139
  pyloric stenosis, 345
  Reye syndrome, 373
  Salmonella spp, 144

Vomiting *(continued)*
  threadworms, 155
  toxic shock syndrome, 131
  trichinosis, 155
  vitamin C toxicity, 65
Von Gierke disease, 83
  gout, 440
Von Hippel-Lindau disease, 495
  chromosome association, 60
  presentation, 655
  renal cell carcinoma and, 568
  tumor suppressor genes and, 218
Von Willebrand disease, 393, **406**
Voriconazole, 194, 195
$\dot{V}/\dot{Q}$ mismatch, **634**, 637
$\dot{V}/\dot{Q}$ ratio, 635
VRE (vancomycin-resistant enterococci)
  daptomycin, 191
  enterococci, 133
  highly resistant, 194
  oxazolidinones, 189
V_{max}, 224
Vulnerable child syndrome, **526**
Vulvar lymphatic drainage, 591
Vulvovaginitis, 149, 177
vWF
  receptor for, 386
  in thrombocytes, 386
  in thrombogenesis, 393

W

WAGR complex, 569
"Waiter's tip" (Erb palsy), 428
Waiver to informed consent, 254
Waiving right to confidentiality, 255
Waldenström macroglobulinemia
  multiple myeloma vs, 409
Walking milestone, 258
Walking pneumonia, 146
Wallenberg syndrome, 484
Wallerian, 465
Wallerian degeneration (neurons), 463
Wall tension, 273
Warfarin, **414**
  adverse effects of, 406
  coagulation cascade, 392
  cytochrome P-450 and, 243
  for DVT, 636
  griseofulvin and, 196
  heparin vs, **414**
  PT measurement, 404
  reversal of, 664
  teratogenicity, 582
  therapeutic index value of, 228
  toxicity treatment, 239, 407
  vitamin K antagonist, 66
Warm autoimmune hemolytic anemia, 401
Warthin-Finkeldey giant cells, 166
Warthin tumors, 359
WAS gene, 113
Waterhouse-Friderichsen syndrome, 324
  meningococci, 138
  presentation, 652
Watershed zones, 206, **472**
Water-soluble vitamins, **61**
Waxy casts, 562, 661
Weakness, 499
Wegener granulomatosis, **302**
  autoantibody with, 111
  as granulomatous disease, 211
  labs/findings, 657, 659
  restrictive lung disease, 639
  RPGN and, 564
Weight gain
  atypical antipsychotics, 543
  Cushing syndrome, 323
  danazol, 622
  duodenal ulcers, 363
  glitazone/thiazolidinediones, 340
  hypothyroidism, 327
  major depressive disorder, 531
  mirtazapine, 546
  sulfonylureas, 340
  valproic acid, 514
Weight loss
  adrenal insufficiency, 324
  anorexia nervosa, 537
  Celiac disease, 657
  cholelithiasis and, 379
  chronic mesenteric ischemia, 369
  colorectal cancer, 371
  diabetes mellitus, 336
  esophageal cancer, 361
  gastric ulcers, 363
  Histoplasma capsulatum, 173
  hyperthyroidism, 327
  major depressive disorder, 531
  malabsorption syndromes, 364
  metformin, 340
  Mycobacterium avium-intracellulare, 173
  orlistat for, 383
  pancreatic cancer, 380
  for PCOS, 609
  polyarteritis nodosa, 302
  polymyalgia rheumatica, 444
  pseudotumor cerebri treatment, 491
  renal cell carcinoma, 568
  sleep apnea, 642
  stomach cancer, 362
  for stress incontinence, 569
  tuberculosis, 136
  Whipple disease, 656
Weil disease, 142
Well-patient care, **258–259**
Wenckebach AV block, 284
Werdnig-Hoffmann disease, 500
Wernicke aphasia, 486
Wernicke area, 471
  stroke effects, 484
Wernicke encephalopathy, 62, 541
Wernicke-Korsakoff syndrome, 481, 541
  vitamin B_1 deficiency, 62
Western blot, 49
  HIV diagnosis, 171
Western equine encephalitis, 163
West Nile virus, 163, 176
Wet beriberi, 62
Wharton jelly, 585
Wheals, 447
Wheezing
  asthma, 638
  bronchial carcinoid tumor, 647
  lung cancer, 647
Whipple disease, 364
  periodic acid-Schiff stain for, 122
  presentation, 656
Whipple procedure
  for pancreatic cancer, 380
White pulp (spleen), 94
Whooping cough
  Bordetella pertussis, 139
  pertussis toxin, 128
Wickham striae, 453
Wide splitting, 277
Williams syndrome
  cardiac defect association, 290
  chromosome association, 60
Wilms tumor, 569
  chromosome association, 60
  dactinomycin for, 418
  neuroblastomas vs, 325
  tumor suppressor genes and, 218
Wilson disease, **378**
  chromosome association, 60
  Fanconi syndrome, 556
  free radical injury and, 210
Winged scapula, 428
Winters formula, 561, 670
Wiskott-Aldrich syndrome, 113
  labs/findings, 660
  X-linked recessive disorder, 56
Wnt-7 gene, 580
Wobble, 34, 36
Wolff-Chaikoff effect, 321, 328. *See also* Jod-Basedow phenomenon
Wolffian duct, 589
Wolff-Parkinson-White syndrome, **283**
Wound healing
  phases of, **211**
  scar/keloid formation, 210
Woven bone, 434
Wright-Giemsa stain, 386
Wright stain, 142
Wrinkles of aging, 48
Wrist bones, **426**
Wrist drop, 427
  lead poisoning, 397
Written advance directives, 255
WT1/WT2 genes, 218
Wuchereria bancrofti, 154, 155

X

Xanthine, 457
Xanthine oxidase, 457
Xanthine oxidase inhibitors, 440, 661
Xanthochromia, 661
Xanthochromic spinal tap, 483
Xanthogranulomatous pyelonephritis, 570
Xanthomas
  familial dyslipidemias, 90
  hyperlipidemia and, 291
Xanthoma striatum palmare, 90
Xenografts, 114
Xeroderma pigmentosum, 37
Xerosis cutis, 62
Xerostomia, 232, 441
X-linked agammaglobulinemia, 112
X-linked dominant inheritance, 55
X-linked recessive disorders
  agammaglobulinemia, 112
  hyper-IgM syndrome, 113
  IL-2R gamma chain defect, 113
  NADPH osidase defect, 113
  Wiskott-Aldrich syndrome, 113
X-linked recessive inheritance, 55
X-ray teratogenicity, 582

Y

Yellow cerebrospinal fluid, 661
Yellow fever, 163, **164**
  liver anatomy and, 352
  vaccine, 107
Yersinia spp
  Gram-negative algorithm, 137
  reactive arthritis, 442
  taxonomy, 121
Yersinia enterocolitica, **141**, 175
Yersinia pestis
  animal transmission, 144
  intracellular organism, 124
Yo antigens, 217
Yolk sac tumors, 611, 618

Z

Zafirlukast, 649
  arachidonic acid pathway, 455
Zaleplon, 515
Zanamivir, 197
Zenker diverticulum, **367**, 665
Zero-order elimination, 226
Zidovudine
  HIV therapy, 199
  mechanism (diagram), 197
Ziehl-Neelsen stain, 122
Zika virus, 167
Zileuton, 455, 649
Zinc, **67**
  Wilson disease, 378
Ziprasidone, 543
Zoledronic acid, 456
Zollinger-Ellison syndrome, **338**
  duodenal ulcers, 363
  gastrin in, 356
  MEN 1 syndrome, 339
  proton pump inhibitors for, 381
Zolpidem, 515
Zona fasciculata, 312, 319
Zona glomerulosa, 312
Zona reticularis, 312
Zonular fibers, 504
Zoonotic bacteria, **144**
Zymogens, 358

NOTES

NOTES

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